Knee Surg Sports Traumatol Arthrosc (2012) 20:423–435
DOI 10.1007/s00167-011-1818-0

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# Biomechanical considerations in the pathogenesis of osteoarthritis of the knee

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Received: 8 August 2011 / Accepted: 22 November 2011 / Published online: 16 December 2011


**Abstract** Osteoarthritis is the most common joint disease and a major cause of disability. The knee is the large joint most affected. While chronological age is the single most important risk factor of osteoarthritis, the pathogenesis of knee osteoarthritis in the young patient is predominantly related to an *unfavorable biomechanical environment* at the joint. This results in mechanical demand that exceeds the ability of a joint to repair and maintain itself, predisposing the articular cartilage to premature degeneration. This review examines the available basic science, preclinical and clinical evidence regarding several such unfavorable biomechanical conditions about the knee: malalignment, loss of meniscal tissue, cartilage defects and joint instability or laxity.
*Level of evidence* IV.

**Keywords** Cartilage · Malalignment · Meniscus · Osteochondral defects · Joint instability · Pathology · Etiology

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## Introduction

Osteoarthritis is the most common joint disease. It is characterized by joint pain and dysfunction and, in advanced stages, joint contractures, muscle atrophy and limb deformity. The knee is the large joint most commonly affected.

The primary changes with osteoarthritis occur in the articular cartilage, followed by associated changes in the subchondral bone [25, 88]. Recently, more focus has been placed on the subchondral bone as the primary cause of symptomatic disease [60, 61, 93, 141]. Understanding of changes early in the development of osteoarthritis (*early osteoarthritis*) is important, since these changes could still be reversible, and therefore, preventive treatment could be initiated to halt or reverse further progression of the disease. This is especially true in the young patient.

The etiology of osteoarthritis is multifactorial and to date not fully understood. Age is the major independent risk factor of osteoarthritis; however, aging and osteoarthritis are inter-related, not inter-dependent [88]. Where cartilage senescence is to some extent part of *normal* aging and the relationship between aging and the development of osteoarthritis is incompletely understood, it is becoming apparent that aging changes in the musculoskeletal system contribute to the development of osteoarthritis by working

in conjunction with other factors, both intrinsic (e.g., alignment, overloading) and extrinsic (e.g., genetics) to the joint [88]. In the young patient, the pathogenesis of knee osteoarthritis is predominantly related to an unfavorable biomechanical environment at the joint, which results in mechanical demand that exceeds the ability of a joint to repair and maintain itself, predisposing the articular cartilage to premature degeneration [26]. The pathophysiology of the process by which joint degeneration leads to the clinical syndrome of osteoarthritis remains poorly understood.

In this review, the pathophysiological mechanisms by which biomechanical conditions about the knee can lead to the development of osteoarthritis are discussed (Table 2), and the relation of distinct clinical conditions about the knee (malalignment, loss of meniscal tissue, cartilage defects and joint instability) and the development and progression of clinical and/or radiographic osteoarthritis are evaluated. In this review, first, normal cartilage structure and function, and histopathological changes with normal aging are discussed. Then, cartilage loading and the pathophysiological impact of overloading are reviewed. The impact of trauma on cartilage is discussed separately. Last, the relation and pathophysiological changes related to distinct unfavorable biomechanical conditions about the knee (malalignment, loss of meniscal tissue, cartilage defects and joint instability) and clinical and/or radiographic osteoarthritis are evaluated.

## Cartilage structure, function and homeostasis

### Normal structure and function

Articular cartilage consists primarily of extracellular matrix with a sparse population of cells, lacking blood vessels, lymphatic vessels and nerves [25, 28]. It has a low level of metabolic activity, and there is little or no cell division or cell death in normal adult articular cartilage, although articular chondrocytes *are* in fact capable of cell division [4, 25, 87, 88, 123]. The chondrocytes, making up only about 1% of volume of adult human articular cartilage [25], is the one cell type present in articular cartilage and, therefore, is responsible for both the synthesis and the breakdown of the cartilaginous matrix [25, 60, 87]. The mechanisms that control the balance between synthesis and degradation remain poorly understood, but cytokines with anabolic and catabolic effects appear to have important roles [25, 60].

For articular cartilage to exert its normal function within the joint, it needs to be elastic and have high tensile strength. The unique mechanical properties of articular cartilage depend on the extracellular matrix [25]. This extracellular matrix consists of two components, tissue fluid and the framework of structural macromolecules consisting of type II collagen fibers, proteoglycans and non-collagenous proteins and glycoproteins, all produced in the appropriate amounts and assembled and organized into a highly ordered molecular framework by the chondrocytes [25, 28]. The collagen matrix gives cartilage its form and tensile strength [25]. Proteoglycans and non-collagenous proteins bind to the collagenous network, help stabilize the matrix macromolecular framework and help chondrocytes bind to the macromolecules of the network [25].

### Osteoarthritis is disruption of homeostasis

Osteoarthritis results from failure of chondrocytes to maintain the homeostasis between synthesis and degradation of these extracellular matrix components [4, 25, 26, 60, 88]. This disruption of homeostasis results in increased water content and decreased proteoglycan content of the extracellular matrix; and weakening of the collagen network due to decreased synthesis of type II collagen and increased breakdown of pre-existing collagen [25]. Furthermore, there is increased apoptosis of chondrocytes. At first, compensatory mechanisms, such as increased synthesis of matrix molecules and proliferation of chondrocytes in the deeper layers of the cartilage, are able to maintain the integrity of the articular cartilage, but eventually loss of chondrocytes and changes in extracellular matrix predominate and osteoarthritic changes develop [25, 28].

### Aging and cartilage

Since there is little or no cell division or cell death in adult articular cartilage, chondrocytes are thought to be long-lived cells and, therefore, can accumulate age-related changes over time [4, 25, 87, 88]. As a consequence, aging profoundly alters chondrocyte function and matrix structure and functioning (Table 1).

There appears to be an age-related reduction in the number of chondrocytes in articular cartilage, but the extent of cell loss is debated [87]. Little data are available about the occurrence of apoptosis in chondrocytes, with the exemption of the finding of increased apoptosis in *rat* cartilage with aging [2]. Telomere shortening, a classic feature of cell senescence, has been observed in chondrocytes [87]. However, since cell turnover is so low, it seems unlikely that these shortened telomeres represent replicative senescence, which generally require more than 30–40 cell replication cycles [67, 88]. Telomere shortening can also result from stress-induced senescence, which seems the more likely mechanism in cartilage, with chronic

inflammation and oxidative stress being offending factors [44, 88] (Table 2).

There is increasing evidence that cell senescence can result in phenotypical alteration of cells, called the *senescent secretory phenotype* [32, 33]. This phenotype is characterized by increased production of cytokines and growth factors. Accumulation of cells expressing this *senescent secretory phenotype* may contribute to tissue aging, by stimulating matrix degradation en reducing matrix synthesis and repair, and possibly even directly link aging to joint degeneration [88].

Chondrocytes become less responsive to growth factors with aging, thereby further reducing matrix synthesis and repair. A decline in response to insulin-like growth factor-I (IGF-I), possibly due to altered signaling, may, due to its important autocrine effect on survival [86], also be implicated in age-related cell death [88].

Age-related changes in size, structure and sulfation of aggrecan, the molecules in cartilage matrix that hold water, have been reported, changing the biophysical properties of cartilage matrix and therefore reducing its resiliency and tensile strength [15, 27, 51, 152].

Furthermore, articular cartilage has a relatively low turn-over rate and is therefore susceptible to accumulation of advanced glycation end-products, resulting from spontaneous nonenzymatic glycation of proteins [146, 147]. Increased collagen cross-linking due to modification of collagen by AGE formation renders the cartilage more brittle with increased fatigue failure [88]. A role in the development of osteoarthritis has been suggested [47, 146].

There is increasing evidence that oxidative stress due to chronic production of endogenous reactive oxygen species (ROS or "free radicals") plays an important role in aging and in the link between aging and osteoarthritis [87–89]. Increased levels of ROS can damage DNA, including mitochondrial DNA, thereby affecting cell viability and contributing to the disruption of extracellular matrix homeostasis [45, 65]. Increased levels of ROS may also contribute to the senescent secretory phenotype [157] and the reduced sensitivity of chondrocytes to IGF-I [156].

**Table 1** Aging changes in joint tissues and the contribution of aging to the development of osteoarthritis

| Aging change | Contribution to OA |
|---|---|
| Accumulation of cells exhibiting the senescent secretory phenotype | Increased cytokine and MMP production stimulates matrix degradation |
| Oxidative stress/damage | Increased susceptibility to cell death and reduced matrix synthesis |
| Decreased levels of growth factors and decreased growth factor responsiveness | Reduced matrix synthesis and repair |
| Increased AGE formation | Brittle tissue with increased fatigue failure |
| Aging change | Contribution to OA |
| Accumulation of cells exhibiting the senescent secretory phenotype | Increased cytokine and MMP production stimulates matrix degradation |

Adapted with permission from: Shane and Loeser [123]

**Table 2** Unfavorable biomechanical conditions about the knee joint and the mechanisms by which they result in relative overloading of the articular cartilage

| Unfavorable biomechanical condition | Mechanism of relative cartilage overloading |
|---|---|
| Malalignment | Abnormal load distribution due to shifting of the center of pressure of the tibiofemoral force, resulting in locally increased stresses on the articular cartilage |
| Loss of meniscal tissue | Alteration in load transmission, resulting in increased peak local stresses on the articular cartilage |
| | (Partial) loss of secondary constraint to anteroposterior translation in unstable (i.e. anterior cruciate ligament-deficient) knees |
| Cartilage lesions | Increased stresses on the lesion rim of diameters greater than 10 mm |
| | Increased exposure of subchondral bone leading to endplate stiffening and microcracks |
| Joint instability or ligament laxity | Abnormal load distribution due to shifting of the center of pressure of the tibiofemoral force, resulting in locally increased stresses on the articular cartilage |
| | Increased translation between articular surfaces, resulting in increased shear stresses on the articular cartilage |
| Trauma | Cartilage damage due to traumatic impact per se |
| | Increased metabolic and oxidative stress of chondrocytes, resulting in accelerated chondrocyte senescence |

As stated earlier, the etiology of osteoarthritis is multifactorial and aging contributes, but does not directly cause osteoarthritis. The various factors that contribute to the development of osteoarthritis by working in conjunction with aging changes are best understood in the way they accelerate the above-discussed so-called 'normal' aging changes: through mechanical damage of the cartilage, through intrinsic modifications in components of the extracellular matrix or of the chondrocytes, or through alterations in cell–matrix interactions. Association of aging and osteoarthritis involves all these elements [77].

## Cartilage loading and overloading

### Cartilage loading and overloading

Joint loading can induce a wide range of metabolic responses in articular cartilage. The mechanisms by which chondrocyte-mediated production of extracellular matrix components responds to mechanical stimuli are only beginning to be understood [25, 26]. There are multiple regulatory pathways by which chondrocytes sense and react to mechanical stimuli, including upstream signaling pathways and mechanisms that may lead to direct changes at the level of transcription, translation, posttranslational modifications, and cell-mediated extracellular assembly and degradation of matrix [25, 64, 139]. Also, there are multiple pathways by which physical stimuli can alter not only the rate of matrix production, but also the quality and functionality of newly synthesized proteoglycans, collagens, and other molecules [25].

Normal synovial joints can withstand repetitive loading during normal activities for a lifetime without developing osteoarthritis [26, 140]. However, mechanical demand that exceeds the tolerance, that is, the ability to repair and maintain itself, of the articular cartilage, plays an important role in the development and progression of joint degeneration in all forms [25, 26]. Excessive mechanical surface contact stress can directly damage articular cartilage and subchondral bone and adversely alter chondrocyte function [26]. In experimental setting, it has been shown that cartilage cannot survive more than 25 MPa of impulsive contact stress. Since physiological peak contact stresses are several fold less, there appears to be a built-in 'safety' factor [26]. The in vivo tolerance of human cartilage to surface contact stress is not known, but an association between high mechanical demand and degenerative changes of the hip joint has been observed. In addition, joint apposition and engagement are important determinants of cartilage damage following an impact event. Also, substantial acute micro-damage (e.g., micro-fractures, cartilage fissures, chondrocytes death, proteoglycan release) can result from impact levels far below the level needed to produce macroscopic fracture. This micro-damage may progress to detectable compromise of the mechanical integrity of the articular cartilage. Furthermore, loading rate [53] and shear stress [11, 12] are important variables.

Many clinical conditions about the knee can result in excessive mechanical demand or *overloading* of the either intact or already damaged articular cartilage: diffusely, due to obesity and high-impact sports; or, more focally, due to uneven load distribution with joint malalignment, after loss of meniscal tissue or at the edges of cartilage defects and post-traumatic joint incongruities.

### Post-traumatic osteoarthritis

Clinical experience shows that the development and progression of post-traumatic osteoarthritis is not necessary due to rapid wear of an irregular articular surface alone [97]. The relationship between residual osseous depression of the joint surface and development of osteoarthritis is very inconsistent. Even when joint congruity, alignment and stability are adequately restored, the joint may degenerate [96]. On the other hand, apparently normal articular surfaces often degenerate following injuries as well [96].

The mechanisms responsible for the development of osteoarthritis following acute injury remain incompletely understood. Experimental work has shown that both pulses of acute energy and chronic mechanical overload damage and cause or accelerate degeneration of this articular cartilage [24]. The theoretical goal of anatomically reconstructing the joint is to decrease joint incongruity, malalignment and instability, thereby avoiding, or at least decreasing, focally elevated contact stresses, which are thought to be in large part responsible for the development of post-traumatic osteoarthritis. However, the in vivo tolerance of articular cartilage to both acutely or chronically increased stress and the potential to repair and remodel itself remain largely unknown [26, 96]. Cartilage metabolism appears to be particularly sensitive to loading rate [24], the effect of which to date has only sparsely been taken into consideration in the experimental work on post-traumatic osteoarthritis.

From experimental data, it is observed that certain patterns of increased mechanical stress, in particular high levels of shear stress, increase production of free oxygen radicals and decrease synthesis of proteoglycans; and that this increased *oxidative* stress on chondrocytes accelerates chondrocyte senescence [97]. It is thus concluded that chondrocyte senescence contributes to the risk of post-traumatic articular cartilage degeneration by decreasing the ability of the cells to maintain and repair the tissue [97]. This *oxidative* stress-related damage is in addition to

damage due to chondrocyte senescence resulting from increased *metabolic* stress resulting from the trauma impact and following the repair response that was already taken place [97]. Experimental studies suggest that, despite its adverse effects on cartilage, a period of non-weight bearing may also have its advantages in that it may be protective against some types of chemically induced damage to chondrocytes [19, 22]. In addition, there is increasing evidence that biological interventions can decrease mechanical stress-induced chondrocyte damage [26, 42, 43, 81].

An interesting and clinically important question is if, and to what extent this mechanism of oxidative stress-related chondrocyte senescence and resulting cartilage degeneration also occurs with altered stress patterns in the joint as seen with malalignment, loss of meniscal tissue, cartilage defects and joint instability. Further studies are needed to shed light on this issue.

## Malalignment, loss of meniscal tissue, cartilage defects and joint instability

### Malalignment

In the normally aligned knee, the center of pressure of the tibiofemoral force passes slightly through the medial side of the knee during stance (average of 4–8 mm medial to the knee joint center) [114], reaching an average peak force of about 3 times body weight (BW) during walking and of about 6 times BW during stair climbing [126, 134]. During flexion, this center of pressure lies even more medial. Varus or valgus malalignment of the lower extremity results in an abnormal load distribution across the medial and lateral tibiofemoral compartment [135]. For example, a 4–6% increase in varus alignment increases loading in the medial compartment by up to 20% [135]. Since axial malalignment increases the stress on the articular cartilage and the subchondral bone, it has been suggested to play an important role early in the development of early osteoarthritis [62]. Indeed, increased knee joint loads are present in patients with knee osteoarthritis [13], and the interaction between axial alignment and dynamic knee joint loading—the loading of the knee joint during gait [8, 18]—is especially pronounced in patients with a high body mass [103]. However, studies examining the relationship between malalignment and early knee osteoarthritis have produced conflicting results.

A possible relationship between the *incidence* of early osteoarthritic changes and axial malalignment is only supported by limited evidence so far. The Multicenter Osteoarthritis Study (MOST) radiographically identified cartilage loss in early osteoarthritis in the same subregions within the knee as subchondral bone attrition [106]. Subchondral bone attrition, characterized by a flattening or depression of the subchondral bone, therefore may indicate an increased load transmitted through the articular cartilage. In patients with varus malalignment, subchondral bone attrition was found in the medial compartment; and in patients with valgus malalignment in the lateral compartment. Brouwer et al. [21] reported an association between valgus and varus alignment and the development of radiographic osteoarthritis of the knee. This relationship was more pronounced in obese patients, compared to the non-obese. Further study of the relation between malalignment, obesity and the development of early osteoarthritic changes is needed.

In contrast, the correlation between the *progression* of early osteoarthritic changes and axial malalignment has been well established. Both conventional radiological [21, 34, 102, 124] and MRI [38, 55] studies found that axial malalignment is a potent risk factor for progression of early osteoarthritic changes in patients with axial malalignment [133]. Importantly, the articular cartilage loss [106] and subchondral bone changes [107] may in turn increase malalignment. Cicuttini et al. [38] reported that the degree of varus knee angle was associated with a reduction in the volume of both femoral and tibial articular cartilage in the medial tibiofemoral compartment of the knee over a 1.9-year follow-up period. Similar results were seen in the lateral tibiofemoral compartment.

The rationale for high tibial osteotomy (HTO) is slowing or preventing early osteoarthritic changes by restoring a more favorable biomechanical situation, thereby reducing local compartmental overload, via correction of malalignment. Clinical experience supports this rationale [72]; however, the long-term effectiveness of HTO for treatment of medial compartment osteoarthritis has not been experimentally confirmed to date. Macroscopical (observations made via arthroscopy) [59, 75, 151] and histological (specimens obtained via punch biopsy) [5] improvements following HTO for unicompartmental osteoarthritis have been reported. However, Koshino et al. [79] showed that no true articular cartilage regeneration occurred, but mere regeneration with fibrocartilaginous tissue. Some authors reported improved outcomes after HTO for medial compartment osteoarthritis of the knee if the malalignment was over-corrected [75, 111, 112, 121, 136]. Birmingham et al. [17] reported on an observational cohort study showing clinically important changes in dynamic knee joint loading and patient-reported measures of pain, function, and quality of life after 2 years after HTO for medial compartment osteoarthritis. Shallberger et al. [120] reported a retrospective study showing slight progression of radiological osteoarthritis an average of 16.5 years following HTO for medial compartment osteoarthritis. Parker et al. reported on

a small case series of 10 patients demonstrating improved T1Gd relaxation times with delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC) [155] at the medial compartment, which is reflective of glycosaminoglycan content, without significant differences in the lateral compartment, suggesting a potential for articular cartilage recovery secondary to an improved biomechanical environment [115].

In conclusion, malalignment seems to be associated with increased occurrence of and faster progression of radiographic osteoarthritic changes. The evidence regarding high tibial osteotomy (HTO) preventing such changes by restoring a more favorable biomechanical environment is inconclusive, but promising results have been reported. Further studies are needed to increase our understanding of and justify this practice.

## Loss of meniscal tissue

Any substantial loss of meniscal tissue from injury or iatrogenic meniscectomy permanently alters the biomechanical and biological environment of the knee joint [82]. Subtotal or total meniscectomy increases the risk of secondary osteoarthritic changes by a factor 14 when compared to matched controls [98, 118], eventually resulting in radiographic changes in 30–70% of patients [6, 31, 119]. The role of concomitant cartilage damage related to the trauma that resulted in meniscal injury in the first place, or of iatrogenic damage related to the meniscectomy procedures, has not been determined, but is likely to play a role as well [142]. Worse outcomes have been reported in younger patients, and especially those with associated articular co-morbidities such as chondral damage, ligamentous instability, and malalignment [29, 94]. Even though surgeons are cognizant of the deleterious consequences of meniscal resection, meniscal preservation is not possible in many cases. In some patients, meniscal allograft transplantation can normalize the biomechanics, providing excellent pain relief and improved function [144]. Several studies have demonstrated potential chondroprotective effects of the meniscal transplant, with slowing, but not complete cessation of degeneration [132, 144]. It has to be noted, however, that a slight mismatch or malposition of the meniscal transplant may lead to peak loading and cartilage degeneration [142]. This section will review the biomechanical, pre-clinical and clinical data on the effects of meniscectomy and meniscal transplantation.

## Meniscectomy

Initially described as vestigial, non-functional tissue, the menisci have since been found to play a vital role in load transmission in the knee. They transmit 50% and 70% of the medial and lateral compartment load, respectively, with the knee in extension [122]. This increases to almost 85% when the knee is flexed to 90° [3]. The menisci also serve as an important secondary restraint to antero-posterior joint translation in unstable knees, that is, knees with deficient anterior cruciate ligament [83, 84]. Biomechanical studies have demonstrated significant alteration in load transmission with meniscal deficiency or mismatch [142]. Removal of the central 1/3 of the meniscus results in a 10% decrease of contact area and 65% increase in peak local contact stresses, while total meniscectomy leads to a 75% decrease in contact area and 235% increase in peak local contact stress [14, 113]. While frank loss of tissue has logical consequences, even a radial tear with otherwise intact tissue reduces or negates meniscal function: a radial tear to within 3 mm of the capsule has the same biomechanical effect as removal of the entire central meniscus up to a 3-mm peripheral remnant [74]. Based on this in vitro study, the meniscus remnant is seen as functional if more than 5 mm wide, and as deficient if less than 3 mm remain undisturbed along the circumferential hoop fibers. Animal experiments have elaborated on these biomechanical theories, demonstrating degenerative changes proportional to the amount of meniscus removed [39].

Biomechanical and animal models of meniscal repair demonstrated near-normal load transmission [14, 109], providing a rationale for meniscal repair when possible. The same study, however, pointed out the challenges posed by radial tears, which even after successful healing demonstrated decreased contact area [109].

Clinical data reflect the biomechanical changes observed experimentally. Radiographic changes in the knee joint after meniscectomy were noticed as early as 1939; however, Fairbank was the first to describe in 1948 a consistent pattern of ridge formation, femoral flattening and joint space narrowing in 107 patients that had undergone open, most likely complete meniscectomy [54]. Jackson in 1968 reviewed 577 meniscectomized knees, demonstrating increasing numbers of patients with degenerative changes and osteoarthritic symptoms with longer follow-up, reaching 67 and 33%, respectively, at 30 years follow-up [73]. These findings were confirmed subsequently by multiple authors, supporting Fairbank's theory that meniscectomy predisposes the knee to osteoarthritis, especially when concomitant injuries or abnormalities are present, such as instability or malalignment [29, 94, 98, 117–119]. Relatively few experimental studies on this subject have been performed in vivo besides Voloshin et al. [148] who were able to demonstrate a 20% reduction in the shock absorption capacity of the knee after meniscectomy.

## Meniscal transplantation

Biomechanical studies have demonstrated improved contact area and peak stresses with meniscal transplantation, ranging from near normal to normal [7, 113, 145]. Furthermore, due to its function as a secondary stabilizer, meniscal transplantation can reduce tibial translation and strain on the ACL to near-normal [128]. Fixation technique [35] and positioning [78, 149], as well as sizing of the meniscal transplant, appear to have important impact on the effectiveness and biomechanical result. Experimental studies of meniscal transplantation in animals have demonstrated a chondroprotective effect. Even though degenerative changes were not completely avoided, they were reduced in comparison to meniscectomized controls [1, 9, 40, 132].

Clinical information is limited to date. Chondroprotective effects of meniscal transplantation were reported with a lower incidence of osteoarthritis seen in transplanted patients than expected from other natural history studies. Verdonk et al. [144] demonstrated no progression of chondral damage in 40% of patients, and progression by only 1 grade in an additional 35% in an average 12-year follow-up study. Overall, patients without malalignment, or with correction through osteotomy, fared better [144]. The optimal fixation techniques and implant positioning remain open issues.

In conclusion, the changes in biomechanical and biological environment of the knee joint following loss of meniscal tissue, either traumatic or following meniscectomy, and the deleterious consequences of those changes on the articular cartilage are well known. There seems to be a rationale for meniscus repair to restore the optimal biomechanical environment whenever possible, however clinical evidence is limited. The same is true regarding the use of meniscal transplantation.

## Cartilage defects

Cartilage lesions are best divided according to their depth into partial-thickness and full-thickens defects. A somewhat distinct category are osteochondral lesions. According to recent studies, partial and full-thickness lesions can progress and even regress from one into another [37, 105]. Partial-thickness lesions are considered less symptomatic, and there is little evidence for their progression onto osteoarthritis [23, 49, 99]. Full-thickness chondral and osteochondral lesions frequently cause symptoms, and they are generally believed to predispose to premature osteoarthritis [20, 23, 68, 69]. The cause of the pain in these patients is probably multifactorial and derived mainly from the subchondral bone and peri-articular tissues, although a local rise in intraosseous pressure may play an important role as well [93, 141]. Early focal lesions seen in aging exhibit molecular changes in the extracellular matrix similar to those observed in osteoarthritis [129]. Moreover, the cartilage from the edge of debrided articular defects was inferior to that from a standard donor site when used for autologous chondrocyte cultivation [95]. Focal chondral and osteochondral lesions are common, and they were encountered in about 20% of knee arthroscopies [41, 70], but also in about 40% of knee MRI's in healthy subjects without a family history of knee osteoarthritis [50]. Not all of these lesions were related to trauma, and a significant proportion of them were asymptomatic. The scientific evidence on which lesions and under what circumstances in the knee would progress to osteoarthritis is limited. An in vitro study on human cadaveric material determined the influence of osteochondral defect size on defect rim stress concentration, peak rim stress, and load redistribution to adjacent cartilage over the weight-bearing area of the medial and lateral femoral condyles [66]. Rim stress concentration was demonstrated for osteochondral defects 10 mm and greater in size. The structural changes in the subchondral endplate might be a precursor for lesion's degenerative progression. As defect size increases, more surface area of exposed subchondral bone is contacted by the opposing articular surface, causing endplate stiffening and microcracks. An in vitro study on bovine condyles established that a critical defect area for the subchondral endplate contact was over 1.61 $cm^2$ for lateral condyle and 1.99 $cm^2$ for medial condyle [57, 66]. Critical defect size is defined as the defect size above which no spontaneous healing occurs. Although the term does not take into account the most important factor of lesion healing response, depth, it is still widely used. The reported critical size defects in animals (given in volumes to allow rough inter-species comparison) range from 18 $mm^3$ in dogs to 142 $mm^3$ in horses [36]. Various animal models have helped us to understand the biology of cartilage repair. However, due to the anatomical and biomechanical differences, the animal models cannot give evidence on the natural history of cartilage defects in humans [10, 125].

Classical long-term osteochondritis dissecans studies have demonstrated knee joint dysfunction and high prevalence of osteoarthritic change after fragment removal [68, 85]. On the contrary, the presence of solitary traumatic lesions did not cause a significant clinical deterioration, nor did their presence significantly influence mid-term follow-up outcome after anterior cruciate ligament reconstruction [71, 154]. Widuchowsky et al. [153] reported no differences in clinical assessment or radiographic osteoarthritic changes between knees with untreated focal cartilage lesions compared to the health controlateral knee. All the studies above bear the limitation of a small defect size from 1.5 to 4.0 $cm^2$ [48, 116]. On the other hand, patients with

arthroscopically diagnosed deep cartilage injuries may show improvement in knee function over time, but the function remained substantially inferior to normal [92]. In addition, non-invasive population MRI studies have demonstrated a significant increase of tibiofemoral cartilage loss over 2 years when solitary lesions were present [50]. All these clinical studies focused on solitary lesions within the healthy normal cartilage. However, in the setting of osteoarthritis, Davis-Tuck et al. en Ciccutini et al. clearly showed progressive enlargement over time on MRI [37, 46].

The most pertinent unanswered issue is if our cartilage defect repair strategies stop or slow down the development or progression of osteoarthritic changes at all. At present, a well-documented prospective follow-up over 10 years for the treatment of cartilage defects is available only on the classical *autologous chondrocyte implantation* (ACI) technique. The repair tissue did not develop the unique mechanical properties of native hyaline cartilage, leaving the rim of the defect exposed to increased stresses. Moreover, the increased synovial markers, which were shown to persist in spite of successful ACI, are indicative of continuing cartilage degeneration [101, 116, 143]. Other treatment options include microfracturing [100], polymer-based autologous chondrocyte grafts [80] and resurfacing the defect with a contoured articular prosthesis [16]. Clinical data with sufficient long-term follow-up are for these modalities not yet available.

In conclusion, cartilage defects, depending on size and location, may give rise to increased stresses at the rim of the defect, thereby locally overloading the cartilage and predisposing to osteoarthritic changes. To date, our understanding of the natural history of cartilage defects and the evidence regarding the optimal treatment strategy remain incompletely understood. Restoring the biomechanical environment to near normal seems of paramount importance,

## Joint instability or laxity

Joint laxity and instability have long been considered to be a strong contributor to the development of post-traumatic osteoarthritis [58, 90, 91, 150]. Nonetheless, the definition of instability remains nebulous. Burstein and Wright defined stability as "the ability of a joint to maintain an appropriate functional position throughout its range of motion" [30]. A joint is then stable if, when moving through a normal range of motion, it can carry the required functional loads without pain, while produce joint contact forces of normal intensity on its articular cartilage surfaces [30]. Joint laxity and instability shift the centrally located primary load bearing area to a more peripheral location, resulting in overloading of part of the articular cartilage. There is a change in both static and dynamic loading, with increased stresses through the articular cartilage [138]. Also, as stated earlier, chondrocytes are particularly sensitive to loading rate [26].

The anterior cruciate ligament (ACL) is the knee ligament most common disrupted [58]. Isolated ACL lesions are uncommon; frequently there is associated injury to other ligamentous structures, the menisci, the articular cartilage or the subchondral plate. Those probably have a major contribution to, but are also by themselves associated with the early development of osteoarthritis [90]. In particular, associated meniscus injury even further compromises joint stability [110]. As stated earlier, the menisci are important secondary constraints to antero-posterior joint translation in unstable, that is, anterior cruciate ligament-deficient knees [52, 104, 127].

Experimental data from rabbit and canine models suggest a correlation with degenerative cartilage changes and joint instability, with no threshold being evident [63, 137]. Also in humans, joint instability has long been empirically recognized as a leading risk factor for the development of osteoarthritis. However, there is insufficient evidence that anterior cruciate ligament reconstruction or meniscus repair halt or prevent the development of osteoarthritis in the long term [90]. Even after adequate ACL reconstruction, 50 to >80% of injured knees show radiographic osteoarthritic changes at 9 years or more follow-up [91, 131]. Even though ACL reconstruction may to large extent restore antero-posterior stability about the knee, there is evidence that excessive tibial rotation still persists during activities that are more demanding that walking [130]. Even small persisting instability (*micro-instability*) may lead to supra-physiological cartilage loading and gradual degeneration [137]. This seems even more so, when ACL reconstruction also allows return to participation in sports, which is usually already associated with high-impact loading by itself [56, 90].

Favorable long-term follow-up outcomes in terms of symptoms, function and radiographic appearance have been reported following non-operative treatment of anterior cruciate ligament injury based on neuromuscular knee rehabilitation [108]. Untreated ACL injuries lead to chronic anterior joint instability; this anterior instability has been shown to be associated with an increasing occurrence of posterior meniscal tears when the instability becomes more chronic [52, 76].

In conclusion, joint instability or laxity seems to play an important role in the development of early osteoarthritis. However, the theoretical advantage of reconstructing joint stability on prevention of the development of osteoarthritis in the long-term has to date not been clearly demonstrated by means of methodologically sound studies with sufficiently long-term follow-up. Those studies are clearly

needed to improve our understanding of and justify our practice regarding ligamentous injury, ACL rupture in particular, about the knee.

## Conclusions

Malalignment, loss of meniscal tissue, cartilage defects and joint instability all seem to be strongly correlated to osteoarthritis in one way or the other. It is important to realize that there are many other etiologies that can cause osteoarthritis, some of which also via mechanically induced pathophysiological changes to the articular cartilage, subchondral bone and other possibly other joint tissues such as, but not limited to, obesity, high-impact sports or labor and neuromuscular dysfunction. Ongoing research efforts will gradually clarify the response of cartilage to mechanical loading and oxidative stress, be it following trauma or related to joint overloading, thereby hopefully allowing us to intercept earlier in the pathophysiological process of osteoarthritis and decreasing the burden of osteoarthritis on society.



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