Articular cartilage: Influence of Aging on Joint Disease

Introduction

Articular cartilage is a highly specialized connective tissue found in diarthrodial joints. The primary role of this tissue is to allow for joint movement while redistributing force imposed on the joint.[1] Its smooth, lubricated design facilitates the transmission of loads to the underlying subchondral bone with a low frictional coefficient. Unlike most tissues, articular cartilage is devoid of blood vessels, nerves and lymphatics and is subject to a harsh biomechanical environment.[1] The safeguarding of articular cartilage is largely dependent on maintaining its organized structure; therefore, the preservation and maintenance of articular cartilage are vital to joint health throughout the lifespan.

Basic Structure and Composition

Articular cartilage is made up of hyaline cartilage and is 2 to 4 mm thick.[1] Unlike most other tissue, cartilage is comprised of primary type II collagen instead of type I. It also contains a dense extra cellular matrix (ECM) which is synthesized by highly specialized cells called chondrocytes. Constituting about 2% of the total volume of articular cartilage[2], these cells play a major role in the development, maintenance, and repair of the ECM. The ECM is primarily composed of water, collagen, and proteoglycans, with other noncollagenous proteins and glycoproteins present in lesser amounts.[3,4] Together, all of these components help to retain water within in ECM, which is critical in maintaining this tissue's structural properties.

The ECM contains different zones with respect to the distance from the articular surface—the superficial zone, the middle zone, and the deep zone (Figure 1).[1] The thin superficial zone is designed to protect the underlying layers from shear stress and makes up roughly 10-20% of the overall thickness.[1] The collagen fibers of this zone are packed tightly and

are arranged parallel to the articular surface. Deep to the superficial zone is the middle zone, which provides a transitional area between the superficial and deep zones. This zone represents 40-50% of the total cartilage volume.[1] In this zone collagen fibers are organized in an oblique fashion to provide a functional line of resistance to compressive forces. Given the high proteoglycan content along with the arrangement of collagen fibers perpendicular to the articular surface, the deep zone is designed to provide the greatest resistance to compressive forces. This zone represents roughly 30% of articular cartilage volume.[1]

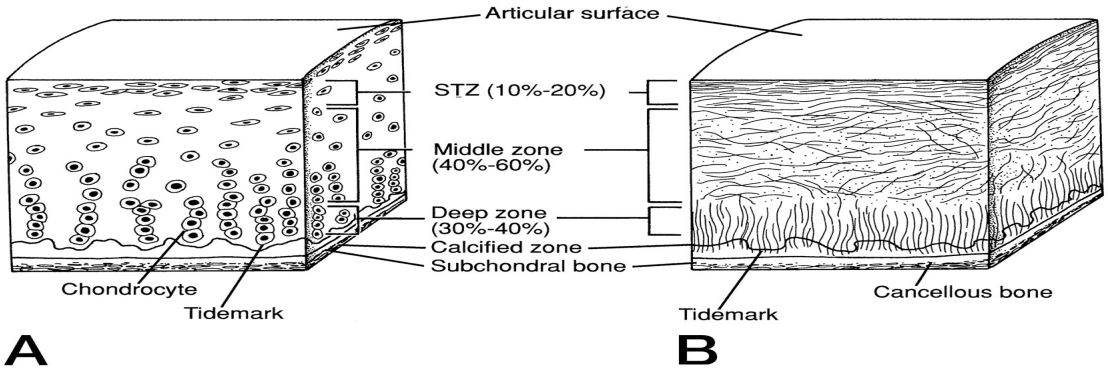

Figure 1

Influence of Aging

Age directly affects the composition of the ECM along with the organization of chondrocytes and their ability to respond to external factors. As individuals grow older, there are changes in zonal structure and distribution of chondrocytes. Although the total number of chondrocytes remains largely unchanged, chondrocytes in the superficial region begin to dissipate while the deeper layer experience an increased number of cells.[1] Findings from Quintero et al[5] suggest an association between viable chondrocyte cell density and maintenance of healthy ECM. This study determined that individuals over 90 years of age with intact knee articular cartilage surfaces are distinguished by a significantly increased number of chondrocytes per tissue volume. Presumably changes in both the ECM and chondrocyte cells act to exacerbate

pathological changes in one another since altered ECM may lead to increased mechanical stress in the cells while cell loss or dysfunction leads to deficient ECM synthesis and increased degradation.[6]

Aging is also associated with a decrease in hydration of the matrix. This leads to an increase in compressive stiffness and decreased ability to attenuate contact forces that cross the joint.[1] This change significantly affects the underlying subchondral bone as the cartilage loses its ability to undergo reversible deformation confirming the need to maintain an optimal ECM environment.

Osteoarthritis and The Consequence Of Aging-Related Changes

While aging-related changes occur in the joint tissue of all individuals, osteoarthritis (OA) does not manifest in all individuals, even with advanced age.[15] This observed pattern suggests that aging does not necessarily cause OA but that aging-related changes provide a foundation upon which OA can be initiated. There is mounting evidence that suggests that the changes that occur in the articular cartilage during the development of OA are the result of a loss in normal homeostasis.[6] In the presence of these changes, a cycle as depicted in Figure 2 is likely to occur.[7]

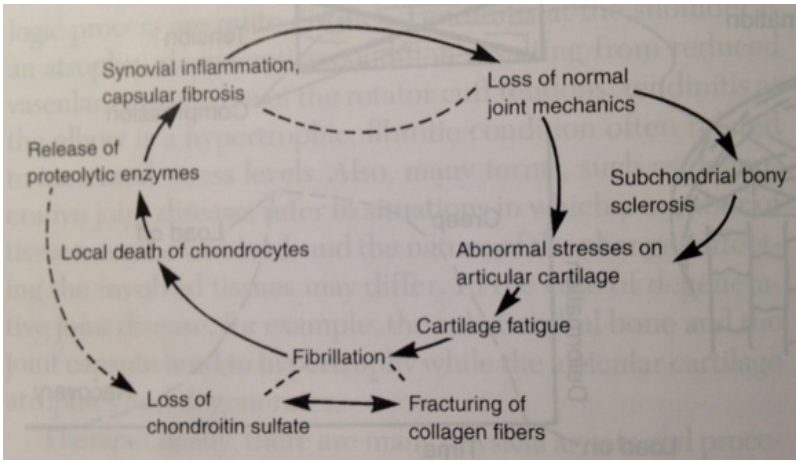

Figure 2: Cycle of degenerative changes in a joint

With aging and OA, the ECM changes in composition and total amount and also undergoes proteolysis. Specifically, it is recognized that OA is directly linked to an increase in water content of the articular cartilage with a decrease in proteoglycan content.[8] The superficial zone is where the earliest changes can be noted which is signified by the development of superficial defects and fibrillation. The superficial region is also most susceptible to mechanical injury. Structural changes in the knee seen in the patella, medial and lateral femoral condyles are correlated with biomechanical dysfunction in cartilage. Concurrent loss of chondroitin sulfate leaves the collagen fibers more susceptible to fracture resulting in a softening of the surface layers, which causes the cartilage to become less able to withstand stress. The areas adjacent to this damage must now absorb the increased stress, causing failure among neighboring tissues.[7]

A highly prevalent change in aging cartilage is the deposition of calcium containing crystals, primarily calcium pyrophosphate (CPP) and basic calcium phosphate (BCP).[9] In the knee this cartilage calcification represents a precursor to increased fibrillation and OA development. A recent study performed by Terkeltaub concluded that calcification correlated with increased disease severity in individuals with end-stage OA.[10] It has also been postulated that the presence of calcium crystals produced by chondrocytes or released into the joint space from adjacent tissues, such as the meniscus, may stimulate chondrocytes to produce inflammatory mediators and ECM-degrading enzymes and thus influence the onset and progression of OA.[10]

The biological mechanisms of OA discussed above lead to cartilage degradation. In order to evaluate the disease level, a subjective grading scale was developed by Kellgren and Lawrence (K&L).[33] This scale grades the severity noted on a radiograph using a scale ranging from 0 to 4, zero being normal and four being severe OA. Markers such as number of

osteophytes, level of joint narrowing, and sclerosis are detectable on the radiograph and are used to define the severity of OA. Table 1 shows the description of each of these levels.[33] Figure 3 displays the K&L grade levels as evident on an example radiograph.[11]

Grade 0	Normal
Grade 1	Doubtful joint narrowing, possible osteophyte
Grade 2	Possible narrowing, definite osteophyte
Grade 3	Definite narrowing, multiple osteophytes, some sclerosis, possible deformity of bone ends
Grade 4	Marked narrowing, large osteophytes, severe sclerosis, definite deformity of bone ends

Table 1: Kellgren and Lawrence grading system for OA

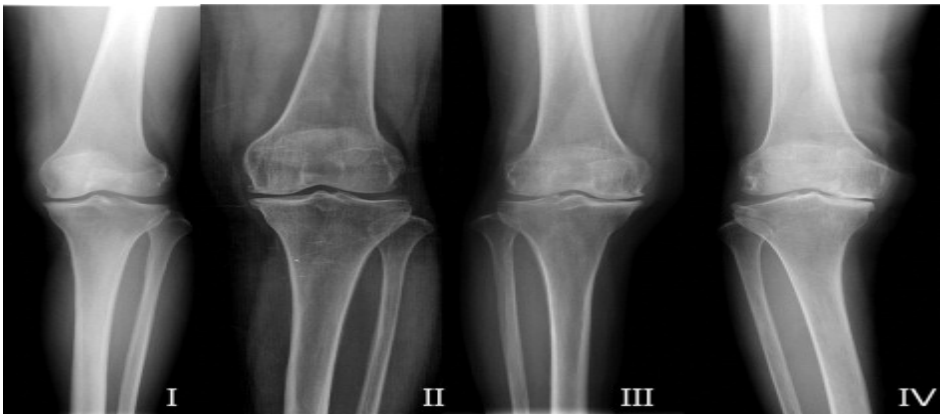

Figure 3: X-rays indicating level 0 (I), level 2 (II), level 3 (III) and level 4 (IV) of Kellgren and Lawrence grading system for OA

Risk Factors

Certain factors have been shown to be associated with a greater risk in the development of osteoarthritis. Findings have implicated several factors, including genetic factors, joint deformity, injury, obesity, and aging in the pathogenesis of osteoarthritis. Researchers suspect that OA is caused by a combination of these factors and the environment.

Genetic factors have been found to be a strong determinant of the disease. Results from a classic twin study conducted by Spector et al[12] concluded that the influence of genetic factors is between 39% and 65% in OA of the hand and knee in women, about 60% in OA of the hip, and

about 70% in OA of the spine. Considered together, these estimations suggest a heritability of OA to be 50% or more, indicating that half the variation in predisposition to this disease in the population is explained by genetic factors.

Results from multiple well-designed studies have demonstrated a statistically significant link between obesity and OA incidence. A case-control study carried out by Coggon and colleagues[13] determined the odds ratio for developing OA was 0.1 when BMI was less than 20 versus 13.6 when BMI was more than 36. Another study showed that the risk for knee OA increased by 36% for every 5 kg of weight gained.[14] Interestingly, weight gain in early adult life, which is recognized as having a BMI of more than 25 at ages 36-40, is markedly associated with cases of knee OA later in life.[15] Fortunately, this factor is modifiable, and it has been determined that each pound of weight lost will result in a 4-fold reduction in the load exerted on the knee per step during daily activities.[35]

Specifically, malalignment of the knee has been assumed to correlate with unicompartmental OA. Studies indicate that varus, valgus, and leg-length discrepancy contribute to the progression of the disease.[16] In fact, Brouwer et al[17] found that increased varus malalignment is associated not only with progression of knee OA, but also with development of knee OA, especially in individuals who are overweight or obese.[19] Furthermore, studies also indicate that a deviation as little as 5° from neutral becomes a risk factor for OA.[20] Severity of malalignment has also been found to correlate with the magnitude of subsequent joint space loss and subsequent functional deterioration.

With respect to aging, the risk of OA increases considerably with each decade after the age of about 45 years[18], with more than 50% of people over 65 demonstrating radiographic changes in the knee that indicate arthritis.[19] The current theoretical framework for the

relationship between aging and OA is that aging of the musculoskeletal system increases the vulnerability to OA but does not directly cause it.[21] Degenerative changes in the meniscus and joint ligaments, increased bone turnover, and the calcification of joint tissues have all been identified as contributing factors in the development of OA in the elderly.

Knee injury has been shown to cause a four-fold increase in the risk of developing knee osteoarthritis.[22] There has been some evidence to suggest that experiencing an acute injury, such as an ACL tear, will lead to faster development of OA in older adults when compared to younger adults.[23] There is speculation that the damaged incurred by the articular cartilage is in response to the decreased ability to protect the joint surface from shearing forces due to increased laxity, which results in abrasion of the cartilage.[24] Meniscal damage is also becoming increasingly accepted as a major risk factor for the development of OA. Ding et al[25] found that presence of a meniscal tear is associated with cartilage defect, loss of cartilage volume, alteration in bone size, and prevalence of radiographic OA. Even if warranted, undergoing meniscectomy may lead to destruction of cartilage and to OA of the knee joint. That being said, it has been suggested that the amount of meniscal tissue removed remains the strongest predictor of long-term onset of OA.[26]

Impact on Quality of Life

Pain and functional impairment are the primary domains that result in a decreased quality of life in those with OA. Among these domains, studies have found that women demonstrate higher scores, indicating more physical disability and higher levels of perceived pain.[27] An analysis of various surveys revealed that among people 65 to 74 years of age, OA was the fifth largest cause of disability in the United States.[28] According to a large study by Guccione et al, daily activities most impacted by OA include heavy home chores (34% disabled), walking 1 mile

(31%), stair climbing (10%), and grocery shopping (10%).[29] Notably, the ability to walk 1 mile and participate in light housekeeping was appreciably more restricted among those with knee OA compared with matched patients with heart disease.

Prevention

When considering preventative options, there is a need to evaluate the presence of risk factors in each individual. There are several modifiable risk factors that increase the risk of developing OA such as obesity, biomechanics of the joint, abnormal loading, occupational factors, sports participation, and muscle weakness. By avoiding these risk factors or reversing their risk, it is possible to positively affect the critical outcomes of preventing damage, preventing or reducing pain, and improving function and activities. Key recommendations for the prevention of OA suggest that individuals should maintain an acceptable level of fitness, avoid obesity, restore normal biomechanics, and consider environmental adaptations to prevent excessive stress.[30,31]

Moreover, recent developments in MRI techniques have allowed for more detailed assessment of the progression of OA. Imaging has also been utilized to identify those at greatest risk for disease progression allowing early intervention and modification of risk factors which may slow the progression.[32,34]

Current Concepts in the Treatment of Articular Cartilage Defects in the Knee

<u>Nonoperative Treatment</u>:

Weight loss

The American Academy of Orthopaedic Surgeons (AAOS) recommends self-management, exercise, and integrated health programs in the treatment of knee OA. Examples of these suggested programs are delineated in Figure 4.[57] Evidence supports a combination of

weight loss with diet and exercise as the current standard in nonoperative management of knee OA.[35] A study by Messier et al[36] determined that a decrease in body weight of 5% in overweight older adults with knee OA improved patient function by 18%, and when combined with dietary modifications function improved by as much as 24%.

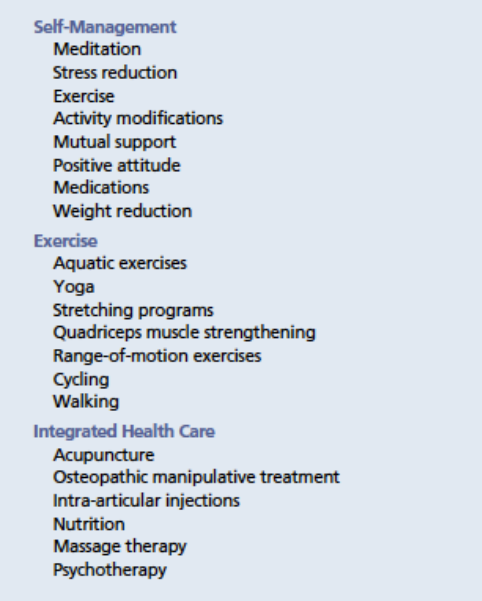

Figure 4: Activity recommendations for patients with primary OA of the knee

Aerobic exercise

Numerous studies have also confirmed that aerobic exercise contributes to improved long-term function in active patients with primary knee OA.[37] In addition, strengthening specific muscles such as the TFL may help to improve knee biomechanics leading to more optimum loading of the joint. Both home exercise programs and group exercise classes have been linked to decreased pain and improved function in patients with knee OA.[37] However, if these exercise regimens are not maintained, the aforementioned benefits will likely be lost within 6 months.[38]

Orthotics

In those with unicompartmental arthritis of the knee, use of orthotics can serve to offload the affected compartment, which may help to delay the need for a surgical procedure. In a review

by Krohn et al[39] the use of lateral wedges were implicated in the treatment of persons with medial compartment OA. In theory, lateral wedges are thought to reduce the external varus moment and thus attenuate medial compartment loading during ambulation. A study by Kerrigan et al[40] concluded that the addition of a 5° or 10° lateral wedge can reduce peak knee varus torque by 6-8%, respectively. Laterally wedged insoles have also been shown to decrease pain in 53-82% of patients with knee OA[42-44] with some studies noting an immediate reduction in walking pain.[41]

Operative Treatment:

There are numerous surgical options available for the treatment of symptomatic, high-grade chondral defects. While patient age, activity level, occupation, and comorbidities are important, detailed assessment and classification of the lesion can also suggest the optimal surgical technique. One accepted treatment algorithm for approaching chondral defects in the knee is shown in Figure 5.[34]

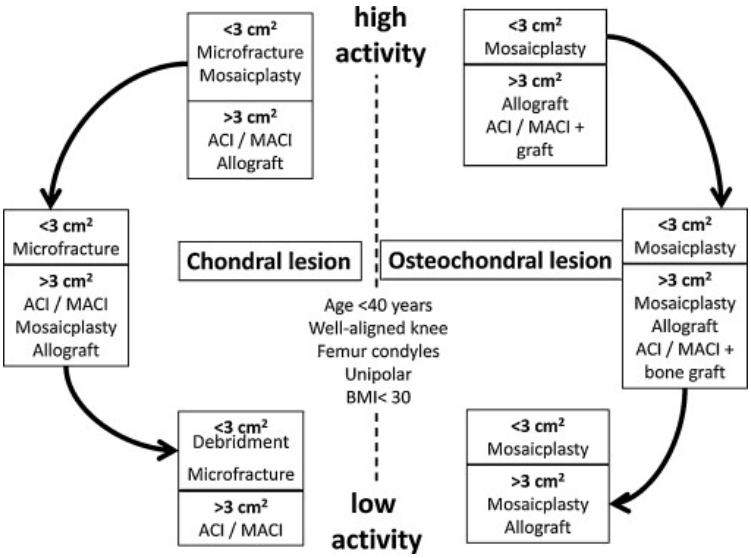

Figure 5: Treatment algorithm for the approach to chondral defects of the knee

Bone Marrow Stimulation techniques

I. Arthroscopic Debridement

This procedure utilizes surgical instruments to remove loose flaps of cartilage that are mechanically impinging the joint. In essence, this procedure evens out irregular joint surfaces changing the loading of the joint to allow for a decrease in abnormal contact pressures. The rationale for preforming arthroscopic debridement is that it may improve symptoms and function, has minimal morbidity, provides a palliative therapeutic procedure, and is thought to forestall the disease process.[45] A cohort involving 204 arthritic knees concluded that 63.2% remained satisfied with the effects of this procedure at a mean of 7.4 years after surgery.[46] Yet another finding of this study, which should be considered, is that 26.5% of patients required at least one further operation within the reported follow-up period. Another study investigating patients with OA found that despite reported relief of symptoms, 15% of these patients progressed to TKA within 1 year.[47] In studies with shorter follow-up, Levy et al[48] noted 100% good or excellent results from simple arthroscopic debridement while Bonamo et al[49] found 83% patient satisfaction at a mean follow-up of 3.3 years.

II. Microfracture

The microfracture procedure is a form of marrow stimulation, similar in concept to debridement. In this procedure a sharp awl perforates the subchondral bone to a depth of approximately 2 mm to 3 mm to induce bleeding.[50] The purpose of this is to recruit mesenchymal stem cells to the surface of bleeding bone. These cells secrete fibrocartilage that will overlay the cartilage lesion. Due to the limited invasiveness of this procedure, other techniques, such as grafting, may still be attempted should microfracture fail. Candidates for microfracture surgery have been identified as younger individuals with isolated lesions, no presence of degenerative changes, and normal knee alignment. It is contraindicated if there is

subchondral bone loss, malalignment, other degeneration, or if the patient is at high risk for being non-compliant with post-operative protocol.[51-53]

Osteochondral Autograft Transfer (OATS)

This procedure involves harvesting of osteochondral plugs from a non weight-bearing surface on the ipsilateral joint. These plugs are then placed in cylindrical holes that have been prepared in the region of the cartilage defect. Benefits of this procedure include no concern for donor site morbidity, and implantation can be performed in a single-stage.[50] A study by Gudas et al[54] found that 93% of patients who underwent the OATS procedure were able to return to their pre-injury level of sports compared with 52% who underwent microfracture. It is important to note that success of this procedure is also dependent on the size of the lesion, patient age, BMI, associated injuries, and length of time that the injury has been present.

Autologous Chondrocyte Implantation (ACI)

ACI involves the harvesting of healthy chondrocytes from a non-weight-bearing surface on the ipsilateral joint. The chondrocytes are then grown in vitro and then implanted at the site of the lesion underneath a protective flap.[55] This procedure aims to generate hyaline cartilage production which closely resembles normal articular cartilage in regards to structural organization and functional properties. ACI is typically preferred in younger individuals (<50) with no concurrent ligamentous instability or meniscal tears and who will be dedicated and compliant with the lengthy rehabilitation process.[64] When comparing ACI to OATS, Horas et al[56] demonstrated similar outcomes with both procedures; however, ACI required a longer recovery. Unfortunately, if an ACI fails, revision is limited to a repeat ACI, OAT or arthroplasty. Studies show occurrence of subsequent surgical procedures following ACI may be relatively

common. In fact, in one study Zaslav et al observed that as many as 49% of patients required a subsequent surgical procedure following ACI.[57]

Arthroplasty

Total knee arthroplasty (TKA), also know as joint replacement, is indicated for disability, pain, limited function from OA or any type or arthritic deformity in the joint space. However, the main indication for TKA remains OA, which accounts for more than 94% to 97% of TKA procedures.[58] The objectives of a TKA include reducing pain, returning to activities of daily living, restoring mechanical alignment, preserving the joint line, and restoring soft tissue balance.[58] Factors such as age and weight must be considered prior to selecting TKA as the treatment of choice. Although not considered a contraindication, both obesity and age younger than 60 have resulted in more variable outcomes following TKA operations.[59] Studies indicate that satisfactory knee function is often restored following a TKA, with the majority of patients able to return to low-impact sporting activity.[60,61] Long-term studies have also confirmed a prosthesis survival rate of 94-94.8% at 10-12 years follow-up.[62,63] It is understood that conservative treatments such as weight reduction, physical therapy, and pharmaceutical treatment should be exhausted prior to TKA.

Conclusion

In conclusion, it is apparent that aging-related changes in articular cartilage increase the risk of joint degeneration and often increase the occurrence of osteoarthritis. It is evident that changes in biological mechanisms significantly increase the risk of cartilage degeneration by decreasing the ability of the cells to maintain and repair the tissue. Furthermore, these changes may adversely affect the outcomes of attempts to repair or regenerate articular cartilage.

Increased understanding of aging and its effects on articular cartilage will lead to better clinical management of the associated risk factors and the resulting degenerative changes.

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