

Osteoarthritis: What does imaging tell us about its etiology.

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**Keywords:** Osteoarthritis, etiology, radiography

## **Abstract**

Osteoarthritis (OA) is the most common joint disorder, and a leading cause of disability. Due to an aging population and increasing obesity the incidence of OA is rising. The etiology of OA is multifactorial and complex thus prevention of OA remains challenging. Risk factors can be divided into person-level factors, such as age, sex, obesity, genetics, race/ethnicity and diet, and joint-level factors including injury, malalignment and abnormal loading of the joints. This narrative review provides a brief overview on the person level risk factors and a more in depth analysis of those at the joint level. It is only through an improved understanding of risk factors for disease that we may be able to meaningfully intervene to prevent its occurrence.

## **Introduction**

Osteoarthritis (OA) is the most common joint disorder affecting approximately 15% of the population, 50% of those over 65 years and 85% of those 75 years or older<sup>[1]</sup>.

OA most commonly affects the hip, knee and hand joints. Given its preference for lower extremity joints, OA is the leading cause of lower extremity disability amongst older adults<sup>[1]</sup>. The risk for disability attributable to knee OA is as great as the risk attributable to cardiovascular disease and greater than that caused by any other medical condition in elderly adults. OA is also the most common reason for a total knee replacement or total hip replacement<sup>[1]</sup>.

As the prevalence of OA is projected to double by the year 2020, due in part to an aging population and an increase in the prevalence of obesity, OA is likely to have a large impact on the health care and public health systems in the future<sup>[2]</sup>. This narrative review provides a brief overview on the person level risk factors and a more in depth analysis of those at the joint level. It is only through an improved understanding of risk factors for disease that we may be able to meaningfully intervene to prevent its occurrence.

### **Defining Osteoarthritis**

OA can be defined pathologically, radiographically or clinically. Due to the ease of standardization and acquisition, radiography is often used as the standard for defining the presence and severity of OA using the Kellgren and Lawrence grading system<sup>[3]</sup>.

It is more clinically relevant to measure individuals with symptomatic OA as not all persons who have radiographic OA have concomitant symptoms, and not all individuals who experience joint symptoms demonstrate radiographic OA<sup>[4]</sup>.

### **Incidence and Prevalence of OA**

Approximately 6.8% of adults aged 26 or older have radiographic hand OA<sup>[5]</sup> whilst 19% of

adults aged 45 or older have radiographic knee OA<sup>[6]</sup> according to the Framingham Osteoarthritis Study. The Johnston County Osteoarthritis Project approximated that 28% of women aged 45 or older had hip OA<sup>[7]</sup>.

The prevalence estimates of symptomatic OA are lower since its presence is defined by a combination of radiographic OA with pain and stiffness in the joint. The Framingham Osteoarthritis Study found that the prevalence of symptomatic knee OA was 7% of adults aged 45 or older<sup>[6]</sup> whilst symptomatic hand OA was approximated at 13.4% and 26.2% in men and women, respectively in adults aged 71 years or older<sup>[5]</sup>. Symptomatic hip OA was present in approximately 10% of the Johnston County cohort<sup>[7]</sup>.

### Risk Factors

OA has a multi-factorial etiology such that a different set of risk factors can act together to cause OA to develop in any given individual. Thus, OA can be considered as the phenotypic manifestation of a series of different pathways leading to a common end-stage pathology (Figure 1).

#### **Person-Level Risk Factors**

##### Age

Age is one of the strongest predictors of OA<sup>[8]</sup>. The exact mechanism/s behind the increased prevalence and incidence of OA with age is poorly understood but is probably a consequence of a combination of biological changes that occur with aging including cellular senescence and exposure to risk factors leading to the joint having a reduced capacity to adjust to biomechanical challenges as a consequence of age related sarcopenia and increased bone turnover.

##### Gender

The prevalence and incidence of OA is higher in females than males with women more often

affected with hand, foot and knee OA than men<sup>[9]</sup>. In addition, women are more likely to suffer more severe radiographic knee OA than men, particularly following the menopause<sup>[9]</sup>. Gender disparities may also be caused by differences in bone strength, alignment, ligament laxity, pregnancy and neuromuscular strength.

#### Racial and Ethnic Disparities

The pattern of joints affected and the prevalence of OA vary amongst racial groups. The National Health and Nutrition Examination Survey 1 suggested higher rates of knee OA in African-American women but not men<sup>[10]</sup>. Results of the Beijing Osteoarthritis Study showed that the prevalence rate of hip and hand OA is less frequent in Asians than white populations<sup>[11]</sup> but that Chinese women had significantly higher prevalence of knee OA than Caucasian women (46.6% vs 34.8%)<sup>[12]</sup>. The factors explaining these differences are poorly understood but likely relate to genetic, environmental, anatomical, and biomechanical features.

#### Obesity

Obesity is a very important risk factor for OA, particularly in the knee<sup>[8]</sup>. Being overweight not only antedates the development of disease but also increases the risk of radiographic progression<sup>[8]</sup>. Men and women with a BMI between 30 and 35kg/m<sup>2</sup> have almost 4.8 and 4 times the risk of knee OA than of men and women with a BMI under 25kg/m<sup>2</sup> respectively<sup>[10]</sup>. For every kilogram of increased body weight, the overall force across the knee in single-leg stance increases four-fold<sup>[13]</sup>.

The Framingham Study showed that weight reduction by 5kg provides a decreased risk for the development of knee OA by 50%<sup>[14]</sup>, confirming that obesity is a modifiable target for prevention of knee OA. Since obesity is increasing in prevalence and is also a risk factor for OA development, it is likely that more individuals will be affected by knee OA in the future.

The relationship between body weight and hip OA is inconsistent and weaker than knee OA<sup>[8, 15]</sup>. Obesity is also associated with hand OA conferring that obesity may also provide some metabolic and inflammatory effects<sup>[16]</sup>.

### Genetics

OA in all of its forms appears to be strongly genetically determined. Genetic factors account for at least 60% of hip and hand OA, with knee OA up to 40%<sup>[17]</sup>. However, OA is a polygenic disease so the overall effect of each individual susceptibility gene is only moderate. Genome wide association studies have identified the growth differentiation factor 5 gene (GDF5) and the 7p22 chromosome as the main contenders for OA susceptibility. Other signals, such as DIO2, SMAD3 and ASPN may also be involved in OA susceptibility.

### Diet

Continuous exposure to oxidant species contributes to the development of age-related diseases, such as OA, by damaging articular tissues<sup>[18]</sup>. High vitamin C intake was shown to reduce the progression of radiographic knee OA threefold as well as reducing the risk of developing knee pain<sup>[18]</sup>. Vitamins D and K are associated with several aspects of bone and articular cartilage metabolism. A diet deficient in vitamins D and K can increase the progression of knee and hip OA whilst an adequate intake of vitamin D might slow disease progression<sup>[19, 20]</sup>. Fish oil contains the polyunsaturated acid omega-3 and this fatty acid has been found to be chondroprotective and an anti-inflammatory agent in *in vitro* studies<sup>[21]</sup>.

## **Joint-Level Risk Factors**

### Occupation

Repetitive joint use has been associated with an increased risk of OA. Studies have found that individuals whose occupations require squatting, kneeling or carrying heavy loads have twice the risk of developing knee OA than occupations that do not require physical

activity<sup>[22]</sup>. Prolonged standing and lifting have also been associated with hip OA<sup>[23]</sup>.

Occupations that require dexterity, particularly repeated use of a pincer grip, have an increased risk of developing OA at the distal interphalangeal and the metacarpophalangeal joints<sup>[24]</sup>.

### Exercise and Physical Activity

The issue of repetitive joint use may also be pertinent for physical activity. Multiple population-based studies<sup>[25, 26]</sup> have found that high levels of physical activity increase the risk of developing knee and hip OA. However, when sporting injuries and joint impact are accounted for there is no evidence to support a deleterious effect of physical activity on normal joints<sup>[27]</sup>.

Conversely, there is an association between developing OA and participating in elite level sport. Elite athletes that participate in repetitive, high intensity and high impact sports (such as running, dancing, tennis, squash and team sports) have an increased risk of developing radiographic hip and knee OA when compared to an age-matched, non-elite cohort<sup>[27]</sup>.

Whether this is solely due to sport participation or as a result of injury is unclear. Thus when considering an individual's risk of developing OA due to exercise the most important aspects to consider are; the type of sport, its intensity and a history of joint injury.

### **Internal Joint Risk Factors**

#### Anterior Cruciate Ligament Injury

The anterior cruciate ligament (ACL) provides the main restraint of anterior tibial translation at the knee and as such is the most commonly injured knee ligament, particularly in sports that require pivoting. The incidence of ACL rupture is 81 per 100,000 annually between the ages of 10 and 64 years<sup>[28]</sup>. For high risk sports, the risk of rupturing the ACL is up to 1000 times higher than the general population<sup>[29]</sup>. The risk of rupture is higher in adolescents than

adults and up to 5 times higher in adolescent women than men<sup>[30, 31]</sup>. Thus, given that the majority of patients that suffer from an ACL injury are adolescents, ACL injuries may lead to a large number of individuals with early-onset knee OA<sup>[29]</sup> as individuals who suffer a knee injury have a 5 times increased risk of developing knee OA<sup>[32]</sup>.

An isolated ACL injury is not common and injury of the ACL is associated with injuries to the cartilage, subchondral bone, menisci and other ligaments<sup>[29]</sup> as shown in Figure 2.

The precise pathogenesis behind why ACL ruptures lead to an increased risk of developing OA and why OA development can be accelerated in injured joints is not known. It has been postulated that the majority of the tissue damage is related to the large forces required to injure the ACL<sup>[33]</sup>. In addition, intra-articular bleeding commonly occurs with the initial injury, as well as the surgical repair, causing both an acute and sustained release of inflammatory cytokines and proteases from joint tissues<sup>[34]</sup> which may lead to further damage of the type 2 collagen network.

Changes in the static and dynamic loading of the injured knee are also apparent due to the lack of a functional ACL. There are significant differences in the tibiofemoral motion of ACL-deficient knees with respect to healthy controls<sup>[35]</sup>. There is increased tibial internal rotation and posterior translation throughout the stance phase of walking altering tibiofemoral loading patterns. This changes the region of cartilage that is in contact during weight bearing causing increased loading of areas that were not conditioned to constant load prior to injury.

Two studies focusing on soccer players found a high prevalence of knee OA in both female<sup>[30]</sup> and male<sup>[36]</sup> athletes. Twelve years after an ACL injury 41% and 51% of men and women exhibited radiographic knee OA respectively. None of subjects reported OA in their non-injured contralateral knee. These results are consistent with a review by Lohmander,



who suggested that 50% of individuals who suffer a traumatic ACL injury develop OA<sup>[29]</sup>.

Yet despite these studies, a 2008 systemic review concluded that the prevalence of knee OA with an isolated ACL rupture was as low as 13%<sup>[37]</sup>. Thus, with such a large range in the prevalence of knee OA attributable to ACL injuries the study methods and outcome measures used to ascertain OA needs to be more consistent across studies.

Studies have also looked at the prevalence of knee OA in subjects that have undergone ACL reconstructive surgery against those that had conservative treatment. Both these treatment groups showed the same prevalence of knee OA<sup>[38, 39]</sup> leading a Cochrane review to declare that there is insufficient evidence to determine which method of treatment is best for ACL injuries<sup>[40]</sup>. A study of European handball players found that 22% of those who returned to their sport post-ACL reconstruction would later reinjure their ACL<sup>[31]</sup>. If long-term joint health is the primary concern this raises questions as to whether returning to sports that involve pivoting is really in the athletes long-term interest with regards to joint health. Consequently it is important to note that whilst surgery may repair the ligament in the short-term it does not prevent the development of knee OA in the long-term<sup>[37, 38]</sup> nor does it protect the knee from re-injury. This highlights that the major intra-articular changes that occur at the time of injury may confer the risk to later OA development.

Paradoxically, knee OA may also cause injury to the ACL. Amin et al<sup>[41]</sup> found that among subjects with established radiographic knee OA between 20-35% had an incidental ACL tear (Figure 3). Established OA may cause degenerative changes within the ACL and thus make it prone to rupture without major trauma. In addition, an ACL tear in established knee OA will accelerate the progression of knee OA<sup>[42]</sup>.

## Injury to the Meniscus

The meniscus plays a protective role in each of the tibiofemoral compartments, acting as a shock absorber and aiding the distribution of load across the joint surface, thus contributing to joint stability and proprioception.

There are two main meniscal lesions; traumatic and degenerative. Traumatic lesions usually occur as a result of an acute trauma in younger, active individuals, are often symptomatic and have been shown to carry an increased risk of developing knee OA<sup>[43]</sup>. Degenerative lesions, as shown in Figure 4, often occur in middle aged and elderly individuals with knees that have already been compromised by OA<sup>[43]</sup>.

An analysis of meniscal lesions found that a greater number of tears occur in the medial than the lateral meniscus (37% vs 16%)<sup>[44]</sup>. Since the medial meniscus is firmly attached to the joint capsule it is more likely to become trapped between the femoral condyle and the tibial plateau under extreme forces. The lateral meniscus is more mobile therefore it is injured less frequently.

The Framingham Study found that 82% of subjects who displayed radiographic knee OA had meniscal damage with the majority suffering from degenerative lesions<sup>[45]</sup>. Bhattacharyya et al found that 91% of subjects who had symptomatic knee OA had a meniscal tear<sup>[46]</sup>. Intra-meniscal signal changes were a frequent finding even when a tear was not present on MRI. These signals may signify the beginnings of meniscal deterioration and thus represent a precursor to a degenerative lesion<sup>[47]</sup>. The long-term radiographic outcome for those subjects with a degenerative lesion has been found to be worse than those with traumatic lesions<sup>[43]</sup> including an increased risk for early onset OA<sup>[29]</sup>.

Recent literature has argued as to whether or not damage to the meniscus is a cause or consequence of knee OA<sup>[48]</sup>. Morphologically normal menisci are rarely found in patients

with knee OA suggesting that there is a strong disorder of the meniscus involved with the development of OA<sup>[45, 46]</sup>. Middle-aged and elderly subjects who have radiographic meniscal damage are at higher risk of developing knee OA, as evidenced in Figure 5, even without cartilage loss, than in subjects who have normal menisci<sup>[49]</sup>. This suggests that damage to the meniscus antedates radiographic cartilage changes. An example of this is the defunctioning of the medial meniscus with a tear at the posterior root with consequent accelerated degeneration<sup>[50]</sup>.

Cartilage destruction due to the pathological processes that are active during the early stages of OA could also affect meniscus and ligament integrity as well. Thus knee OA may also cause meniscal lesions and act to further accelerate the disease<sup>[51]</sup>.

Surgery is the most common form of treatment for injuries to the menisci. However, just like ACL reconstructions, surgery might be able to fix the meniscus in the short-term but it cannot prevent the incidence of symptomatic radiographic knee OA, regardless of whether a total or partial meniscectomy is performed<sup>[43, 49]</sup>. Meniscal replacement surgeries including the use of allogeneic, xenogeneic and artificial menisci have been tried in younger patients but the transplant survival is variable and long-term results are lacking<sup>[29]</sup>.

### Cartilage

Articular cartilage is both aneural and avascular thus cartilage is unable to produce pain, stiffness, inflammation or any other symptom of OA<sup>[52]</sup>. OA was once considered a primary disorder of the articular cartilage but now it is widely appreciated that multiple structures are involved and affected in the development of OA.

Cartilage pathology in OA is a balance between synthesis and degradation of the articular cartilage matrix. Excessive matrix degradation increasingly overwhelms matrix synthesis due to an excess of inflammatory, catabolic signals, matrix metalloproteinases (MMPs) and

aggrecanases which act to further degrade the cartilage matrix<sup>[52, 53]</sup>.

Adult chondrocytes rarely divide thus they can accumulate reactive oxidative species which can cause altered cell viability and chondrocyte death. Recent evidence suggests that during the development of OA there is increased cell proliferation and an up regulation of synthetic activity resulting in clusters of chondrocytes<sup>[52, 53]</sup>. Despite this, these cells are not able to maintain the integrity of the cartilage matrix, mainly due to their inability to respond to growth factors, and thus further contribute to the increased matrix degradation and the destruction of type II collagen<sup>[52, 53]</sup>. These changes are also accompanied by cartilage surface fibrillation and the production of fibrocartilage<sup>[53]</sup>.

It has previously been suggested that cartilage thinning posed an increase risk for OA and may in fact represent the initial pathology of OA<sup>[54]</sup>. However, recent studies suggest that early osteoarthritic cartilage may be thicker and swollen with water due to disruption of the collagen network along with altered proteoglycans. It was proposed that focal areas of denuded cartilage and increased cartilage thickness may be part of the initial evolution of the disease and that cartilage defects may occur in early knee OA and precede cartilage volume loss<sup>[55, 56]</sup>. In patients with symptomatic OA, progression of cartilage defects over 30 months was found in 46% and 22% for the medial and lateral tibiofemoral compartments respectively. Furthermore, cartilage defects are also associated with bone expansion, bone marrow lesions (BML), meniscal injuries and ACL rupture suggesting that they have multiple causes<sup>[56]</sup>. MRI is able to capture these initial structural (and occasionally ultrastructural) changes in the earliest phases of the disease whilst changes such as joint space narrowing as detected by radiographs emerge at a much later stage<sup>[56]</sup>.

### Subchondral Bone

Bone cells are more able to self-repair and modify their surrounding extracellular matrix

than articular cartilage<sup>[52, 53]</sup>. Subchondral bone undergoes adaptations during the development of OA including increase in subchondral plate thickness, sclerosis, joint space narrowing, reduced matrix mineralisation, increased cancellous bone volume, formation of osteophytes at the joint margins, development of bone cysts and advancement of the tidemark associated with vascular invasion of the calcified cartilage. These changes may cause alterations in the adjacent joint surfaces, which in turn will change the joint congruity and hence progress the disease<sup>[53, 57]</sup>.

It is the adaptive capacity of bone that underlies the more rapid appearance of detectable skeletal changes, especially after joint injuries or with altered mechanics. The presence of bone marrow lesions (BML) correlates with the severity of pain as well as the areas of greatest cartilage loss<sup>[53, 57]</sup> (Figure 6). BML were present in 77.5% of subjects who experienced painful knees compared with only 30% of subjects who reported no knee pain<sup>[57]</sup>. Furthermore, BML have been found to be compartment-specific for cartilage progression. In terms of bone abnormalities, BML is the only effective risk factor for predicting knee OA progression<sup>[57]</sup>.

Recent studies<sup>[58, 59]</sup> in asymptomatic populations discovered that the development of new BML in knees that contained no BML at baseline were associated with the progression of tibiofemoral cartilage defects and loss of cartilage volume reflecting early cartilage pathology. This suggests that not only can BML propagate OA progression but also may play an important role in the pathogenesis of knee OA.

### Synovitis and Effusion

Synovitis and effusion are frequently present in OA and are directly responsible for several clinical symptoms and reflect the structural progression of the disease<sup>[54]</sup> (Figure 7).

Synovial inflammation is focused in areas adjacent to damaged cartilage and bone and can

cause the release of proteinases, inflammatory cytokines, MMPs and aggrecanase<sup>[54]</sup> that further accelerates the degradation of cartilage. The releases of these inflammatory mediators, as well as the formation of osteophytes may act to irritate sensory nerve endings within the synovium causing pain. MRI analysis of subjects with knee OA showed that synovial thickening was greater amongst subjects who experienced knee pain than in asymptomatic subjects<sup>[60]</sup>.

The clinical symptoms of inflammation along with the presence of histological inflammation in synovial tissue and cartilage lesions at the border of inflamed synovium are strong indicators that synovitis plays a pivotal role in the development of OA. Synovial inflammation also perpetuates disease progression as Roemer et al<sup>[61]</sup> reported that individuals who displayed moderate to severe baseline synovitis had an increased risk of rapid cartilage loss.

## **Mechanical Factors**

### Quadriceps Strength

Quadriceps femoris is the primary anti-gravity muscle of the lower limb and serves to decelerate the lower limb during ambulation as well as to stabilise the knee.

Quadriceps weakness is common amongst OA patients. Baseline knee extensor strength was reduced in women with no knee radiographic changes at the initial examination but developed knee OA 30 months later<sup>[62]</sup>. This was confirmed by Baker et al<sup>[63]</sup> who found that subjects with asymptomatic patellofemoral and tibiofemoral radiographic knee OA had reduced quadriceps strength when compared to subjects who did not have OA.

Additionally, quadriceps weakness may also increase the risk of structural damage. For every 5kg increase in extensor strength Slemenda et al, found an associated 20% and 29% reduction in the odds of developing radiographic knee OA and symptomatic knee OA

respectively<sup>[62]</sup>.

### Alignment

A shift from neutral will alter load distribution across the knee thus malalignment may contribute to abnormal mechanical forces. Knee malalignment is one of the strongest predictors of knee OA progression. A prospective cohort study showed that abnormal alignment was strongly associated with increased structural degradation in the compartment that was under greatest compressive stress<sup>[64]</sup>. Medial progression of knee OA was four times more likely in individuals with varus alignment, whilst lateral progression was five times more likely in individuals with valgus alignment<sup>[65]</sup>. BML as well as rapid cartilage loss displayed on MRI have also been associated with knee malalignment<sup>[66]</sup>. It is important to note that no study as yet has documented the slowing of disease progression when alignment is corrected.

The association between incident knee OA and malalignment is less apparent. The Rotterdam Study found that individuals with varus and valgus knee alignment had an OR of 2.06 and 1.54 of developing radiographic knee OA respectively<sup>[67]</sup>. However, these results were not supported by the Framingham Study<sup>[68]</sup>.

### **Summary**

As the prevalence of OA in the population continues to rise so does the substantial burden that is placed on the health care system. The etiology of OA is multifactorial and complex thus prevention of OA remains challenging. Risk factors for developing OA are different for each joint. The use of advanced imaging, the measurement of systemic and local biomarkers, combined with the improved methods of measuring symptoms will ultimately help lead to the development of disease-modifying pharmaceuticals and improved non-pharmacologic treatments of OA.

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