1. Epidemiology of osteoarthritis

Frédéric Massicotte
Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM)
Notre-Dame Hospital, Montreal, Quebec, Canada

Abstract. Osteoarthritis (OA) is a progressive multifactorial disease that not only leads to articular cartilage loss and joint space narrowing, but also to pain, loss of function and physical disability, thus greatly impairing quality of life. The concept of the pathology of OA has evolved from being viewed as cartilage-limited to a multifactorial disease affecting the whole joint. Indeed, all the joint tissues including capsule, ligament, tendons, menisci, subchondral bone, synovium, muscle, and neurological structure are intricately implicated in the disease pathology. This chapter will review, from an epidemiological point of view, the classification and radiological definition of osteoarthritis, its socioeconomic burden, the prevalence of radiographic and symptomatic hand, knee and hip OA, and finally the local and systemic risk factors.

Introduction: Osteoarthritis from past to present

Not many diseases can claim to have a history as rich and ancient as osteoarthritis (OA). From prehistoric times to the present day, OA has proven to be a most challenging disease. OA can be traced back in time from paleopathological findings in skeletal remains, historical depictions, and more
recent pathological concepts. In fact, OA is frequently referred to as the oldest known disease on the planet. Indeed, evidence of its presence can be found in dinosaur skeletons of up to 70 million years old [1]. Some more controversial reports even describe the first example of OA in the spine of a 200 million year old Dimetrodon [2]. Osteoarthritis stigmata can be found in nearly every period and civilization, such as in the Neanderthal [3] and Cro-Magnon skeletons [4], Egyptian mummies [5], and more recent skeletal remains from England [6]. The pathological changes in a 100 million year old bone and a contemporary bone are remarkably similar, suggesting that OA is impervious to evolution [7].

As eloquently reviewed by Buchanan et al. [8], despite the nearly ubiquitous presence of the disease throughout evolution, clinicians did not recognize OA until the late 18th century, possibly due to the disease showing few obvious clinical signs. The first report of this disease in the literature may be found in Heberden’s notice of “Digitorum Nodi” in 1782, which was not published until 1802. In the “Commentaries on the History and Cure of Diseases” in 1793 Heberden the Elder described what is now called Heberden’s node with a clear distinction from gout [9]. Further nomenclature confusion delayed the recognition of OA, and OA and rheumatoid arthritis were even considered the same entity, known as arthritis deformans. It was not until 1859, when Alfred Baring Garrod proposed the name rheumatoid arthritis, that a distinction was made between these two diseases [10].

From an epidemiological perspective, the historical reference to OA is controversial, due in large part to the terminology used and the confusion between primary and secondary OA, as well as mimickers such as gout and rheumatoid arthritis. Today, nomenclature debates persist between osteoarthrosis, degenerative bone disease, and osteoarthritis, reflecting the different ideologies on the importance of inflammation in the pathophysiology of OA. However, evidence of the critical role of inflammation in OA is overwhelming and is discussed in Chapter 4 - Proteinase-activated receptor-2: an attractive DMOAD target for the treatment of osteoarthritis.

Classification of osteoarthritis

Considering the high prevalence and socioeconomic impact of OA, well-designed fundamental and clinical studies are of the utmost importance. One of the first steps toward reproducible studies is universally accepted classification criteria. It may seem trivial, but these criteria are continually evolving, for example with the creation of different radiographic scoring systems, which make study comparison a real challenge. To date, the most widely accepted classification criteria are those of the American College of
Epidemiology of osteoarthritis

Table 1. American College of Rheumatology criteria for classification of osteoarthritis.

<table>
<thead>
<tr>
<th>Idiopathic</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized</td>
<td>Post-traumatic</td>
</tr>
<tr>
<td>1. Hands: e.g., Heberden’s and Bouchard’s nodes (nodal), erosive interphalangeal arthritis (non-nodal), scaphometacarpal, scaphotrapezial</td>
<td>Congenital or developmental diseases</td>
</tr>
<tr>
<td>2. Feet: e.g., hallux valgus, hallux rigidus, contracted toes (hammer/cockup toes), talonavicular</td>
<td>1. Localized</td>
</tr>
<tr>
<td>3. Knee</td>
<td>a. Hip diseases: e.g., Legg-Calve-Perthes, congenital hip dislocation, slipped capital femoral epiphysis, shallow acetabulum</td>
</tr>
<tr>
<td>a. Medial compartment</td>
<td>b. Mechanical and local factors: e.g., obesity (?), unequal lower extremity length, extreme valgus/varus deformity, hypermobility syndromes, scoliosis</td>
</tr>
<tr>
<td>b. Lateral compartment</td>
<td>2. Generalized</td>
</tr>
<tr>
<td>c. Patellofemoral compartment (e.g., chondromalacia)</td>
<td>a. Bone dysplasias: e.g., epiphyseal dysplasia, spondylo-apophyseal dysplasia</td>
</tr>
<tr>
<td>4. Hip</td>
<td>b. Metabolic diseases: e.g., hemochromatosis, osteorosis, Gaucher’s disease, hemoglobinopathy, Ehlers-Danlos disease</td>
</tr>
<tr>
<td>a. Eccentric (superior)</td>
<td>Calcium deposition disease</td>
</tr>
<tr>
<td>b. Concentric (axial, medial)</td>
<td>1. Calcium pyrophosphate deposition disease</td>
</tr>
<tr>
<td>c. Diffuse (coxae senilis)</td>
<td>2. Apatite arthropathy</td>
</tr>
<tr>
<td>5. Spine (particularly cervical and lumbar)</td>
<td>3. Destructive arthropathy (shoulder, knee)</td>
</tr>
<tr>
<td>a. Apophyseal</td>
<td>Other bone and joint disorders:</td>
</tr>
<tr>
<td>b. Intervertebral (disc)</td>
<td>E.g., avascular necrosis, rheumatoid arthritis, gouty arthritis, septic arthritis, Paget’s disease, osteopetrosis, osteochondritis</td>
</tr>
<tr>
<td>c. Spondylitis (osteophytes)</td>
<td>Other diseases</td>
</tr>
<tr>
<td>d. Ligamentous (hyperostosis [Forestier’s disease, or DISH])</td>
<td>1. Endocrine diseases: e.g., diabetes mellitus, acromegaly, hypothyroidism, hyperparathyroidism</td>
</tr>
<tr>
<td>6. Other single sites: e.g., shoulder, temporomandibular, sacroiliac, ankle, wrist, acromioclavicular</td>
<td>2. Neuropathic arthropathy (Charcot joints)</td>
</tr>
<tr>
<td>Generalized: includes 3 or more areas listed above (Kellgren-Moore)</td>
<td>3. Miscellaneous: e.g., frostbite, Kushin-Beck disease, Caisson disease</td>
</tr>
</tbody>
</table>

DISH, diffuse idiopathic skeletal hyperostosis
From Altman RD et al. [11]

Rheumatology (ACR). As shown in Table 1, the ACR has classified OA into two broad categories: idiopathic, which can be localized or generalized, and secondary [11]. Secondary OA may further be classified as post-traumatic, congenital, or due to calcium deposition disease or other bone/systemic diseases. As shown in Table 2, specific classification criteria for the hand, hip and knee were also proposed by the ACR, and these criteria are currently used for OA definition in the vast majority of clinical studies [11-13].
**Table 2.** American College of Rheumatology criteria for osteoarthritis of the hand, hip and knee.

<table>
<thead>
<tr>
<th></th>
<th>Clinical</th>
<th>Items required for OA presence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hand</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clinical</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. Hand pain, aching or stiffness for most days of prior month</td>
<td>1, 2, 3, 4 or 1, 2, 3, 5</td>
</tr>
<tr>
<td></td>
<td>2. Hard tissue enlargement of $\geq 2$ of 10 selected hand joints*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. MCP swelling $\leq 2$ joints</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Hard tissue enlargement of $\geq 2$ DIP joints</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. Deformity of $\geq 1$ of 10 selected hand joints</td>
<td></td>
</tr>
<tr>
<td><strong>Hip</strong></td>
<td>Clinical and Radiographic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. Hip pain for most days of the prior month</td>
<td>1, 2, 3 or 1, 2, 4 or 1, 3, 4</td>
</tr>
<tr>
<td></td>
<td>2. ESR $\leq 20$mm/h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Radiographic femoral and/or acetabular osteophytes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Radiographic hip joint space narrowing</td>
<td></td>
</tr>
<tr>
<td><strong>Knee</strong></td>
<td>Clinical</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. Knee pain for most days of prior month</td>
<td>1, 2, 3, 4 or 1, 2, 5, or 1, 4, 5</td>
</tr>
<tr>
<td></td>
<td>2. Crepitus on active joint motion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Morning stiffness $\leq 30$ min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Age $\geq 38$ years old</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. Bony enlargement of the knee on examination</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clinical and Radiographic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. Knee pain for most days of prior month</td>
<td>1, 2 or 1, 3, 5, 6 or 1, 4, 5, 6</td>
</tr>
<tr>
<td></td>
<td>2. Osteophytes at joint margins</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Synovial fluid typical of osteoarthritis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Age $\geq 40$ years old</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. Morning stiffness $\leq 30$ min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6. Crepitus on active joint motion</td>
<td></td>
</tr>
</tbody>
</table>

* 10 selected hand joints include bilateral 2nd and 3rd proximal interphalangeal joints, 2nd and 3rd distal interphalangeal joints and 1st carpometacarpal joints.

DIP, distal interphalangeal; ESR, erythrocyte sedimentation rate; MCP metacarpophalangeal. Adapted from Altman RD et al. [11-13].
Table 3. Kellgren-Lawrence radiographic scoring system for osteoarthritis.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Classification</th>
<th>Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td>No feature of OA</td>
</tr>
<tr>
<td>1</td>
<td>Doubtful</td>
<td>Minute osteophyte, doubtful significance</td>
</tr>
<tr>
<td>2</td>
<td>Minimal</td>
<td>Definite osteophyte, unimpaired joint space</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
<td>Moderate diminution of joint space</td>
</tr>
<tr>
<td>4</td>
<td>Severe</td>
<td>Joint space greatly impaired with sclerosis of subchondral bone</td>
</tr>
</tbody>
</table>

Adapted from Kellgren and Lawrence [14]

The sensitivity and specificity for the hip (91% and 89%), knee (91% and 86%) and hand (92% and 98%) of these criteria are high enough to differentiate OA from more inflammatory arthritis, but are somewhat limited with regard to the discernment of early OA.

The most commonly accepted grading system for radiographic OA was proposed by Kellgren and Lawrence (KL) in their atlas of standard radiographs more than 40 years ago [14]. As shown in Table 3, this scoring system is based primarily on osteophyte presence, with the more severe grades based on the progressive appearance of joint space narrowing and subchondral bone sclerosis. However, multiple studies have criticized this grading system. Indeed, poor correlation between pain and radiographic OA [15], and between high risk for disease progression and low KL grade [16] have been demonstrated. Magnetic resonance imaging (MRI), a newer imaging modality in quantifying articular structures which can overcome some of the pitfalls of X-rays, may become the modality of choice for future clinical trials. However, high price and limited access are still limiting its use.

Socioeconomic burden of osteoarthritis

Arthritis and other rheumatic conditions are becoming a major public health problem and the foremost cause of disability in the developed countries. For example, in the United States in 2002, nearly 43 million adults were affected [17]. Direct and indirect costs attributable to arthritis and other rheumatic conditions totalled an estimated $86 billion in 1997, accounting for nearly 1% of gross domestic product [18]. In the National Health Interview Study, OA and related disorders were the third leading chronic condition causing work limitation (1.6 million people or 8.3% of main conditions of impairment), just after heart disease (10.9%) and back disorder (21.1%) [19].
Osteoarthritis is the most common form of arthritis, affecting a conservatively estimated 27 million Americans in 2008 [20]. Although OA is one of the most prevalent diseases in our aging population, its socioeconomic impact may not have been accorded adequate attention. Despite being less disabling than rheumatoid arthritis, OA poses a greater socioeconomic impact due to its prevalence estimated to be at least 7 to 20 times greater than rheumatoid arthritis [21, 22]. The impact of arthritis on health related quality of life is major [23]. About 80% of patients with OA have movement limitation. According to the National Health and Nutrition Examination Survey III (NHANES III) data, 25% of patients cannot perform major activities of daily living and about 12% require help with personal care and routine needs. Moreover, the real burden of this disease on society is difficult to evaluate since OA patients often have multiple comorbidities and OA can also be confused with other inflammatory diseases [24]. Given the prediction that, by the year 2030, 25% of adults in the United States will have physician-diagnosed arthritis (predominantly OA) [25], it is imperative to quantify its direct (e.g. health care costs) and indirect (e.g. labour productivity) costs.

Reviews on the direct costs of OA vary greatly, with up to a 10-fold difference reported among studies [26]. Nonetheless, data from a multivariate analysis of the relationship between OA and health care expenditure showed that OA increased aggregate expenditure by $185.5 billion per year [27]. Women accounted for $118 billion and men $67.5 billion. Part of this amount comprises indirect costs due to absenteeism, for which OA expenditure is approximately $500 annually per capita, which is equivalent to approximately 3 lost workdays. Aggregate annual absenteeism costs are $10.3 billion (women $5.5 billion, men $4.8 billion) [28].

In 1997, OA was responsible for 55% of all arthritis-related hospitalizations in the United States, with over 400,000 hospitalizations [29]. Together, total knee and hip joint replacements accounted for 35% of the procedures during hospitalization for arthritis [30]. With increasing prevalence due to an older population, nearly twice as many total knee replacements were performed in 2000 compared to 1990 [31]. In 2004, OA led to 97% of the 455,000 knee replacements and 83% of the 233,000 hip replacements [32]. Furthermore, OA accounts for approximately 6% of all arthritis-related deaths, and 0.3 deaths per 100,000 population (or 500 deaths per year) [33]. Moreover, these numbers are likely highly underestimated since gastrointestinal bleeding due to treatment with non-steroidal antiinflammatory drugs (NSAIDs) was not included.
Prevalence of osteoarthritis

In adults, the leading cause of disability is arthritis [22]. The number of arthritic persons and the ensuing social impact are projected to increase by 40% in the next 25 years [25]. In 2008, the National Arthritis Data Workgroup addressed this issue and produced the best available report on the prevalence of OA in the United States. They estimated that 46 million American adults (21% of the population) had arthritis, of whom nearly 27 million had clinical OA (hand, hip, knee, overall), an increase of nearly 30% since 1995 [20]. In comparison, rheumatoid arthritis affected 1.3 million adults, a decrease of nearly 60% since a 1995 estimate.

As radiographic changes and clinical symptoms do not correlate well, these manifestations must be evaluated separately. In addition, as recently reviewed by Zhang et al. [34], the prevalence of OA is variable depending on the definition, the joint, and the population under study. Nonetheless, advanced age and female gender are major risk factors for OA (Table 4).

**Table 4.** Prevalence of radiographic and symptomatic osteoarthritic joint by age and sex from population-based study*.

<table>
<thead>
<tr>
<th>Anatomic site, age</th>
<th>Male (%)</th>
<th>Female (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Radiographic†</td>
<td>Symptomatic</td>
<td>Radiographic†</td>
</tr>
<tr>
<td>Hands ≥26†</td>
<td>25.9</td>
<td>3.8</td>
<td>28.8</td>
</tr>
<tr>
<td>Knees ≥26†</td>
<td>14.1</td>
<td>4.6</td>
<td>13.7</td>
</tr>
<tr>
<td>Knees ≥45†</td>
<td>18.6</td>
<td>5.9</td>
<td>19.3</td>
</tr>
<tr>
<td>Knees ≥45†</td>
<td>24.3</td>
<td>13.5</td>
<td>30.1</td>
</tr>
<tr>
<td>Knees ≥60†</td>
<td>31.2</td>
<td>10.0</td>
<td>42.1</td>
</tr>
<tr>
<td>Hips≥45†</td>
<td>25.7</td>
<td>8.7</td>
<td>26.9</td>
</tr>
</tbody>
</table>

Adapted from Lawrence RC et al. [20]

*Estimates represent prevalence per 100 persons age-standardized to the projected 2000 Census population except for National Health and Nutrition Examination Survey III (NHANES III) estimates, which were adjusted to the 1980 Census population.

†Radiographic knee OA based on anteroposterior projections

1 Framingham OA study [35]
2 Framingham OA study [36]
3 Johnston County OA Project [37]
4 National Health and Nutrition Examination Survey III (NHANES III) [38]
5 Johnston County OA project [39]

Prevalence of hand osteoarthritis

As with the other joints, the prevalence of radiographic hand OA varies depending on the definition, and in a population-based study, it was as high as 29%-76% [40]. In the Framingham study, the overall prevalence of
radiographic hand OA was 27.2% in subjects over 26 years of age [35]. As with the knee, slightly more women than men were affected. In the Rotterdam study, 67% of the women and 55% of the men over 55 years old were reported to have radiographic OA in at least one hand joint [40]. Distal interphalangeal (DIP), thumb base, and proximal interphalangeal (PIP) joints were affected in 47%, 36%, and 18%, respectively. Moreover, polyarticular hand OA (thumb base, DIP, PIP) was more common than single joint disease.

Interestingly, even though radiographic hand OA is extremely common in older subjects, the prevalence of symptomatic hand OA is much lower. In the Framingham study, 3.8% of men and 9.2% of women over 26 years of age had symptomatic OA [35]. DIP (2.9%) and thumb base (2.8%) were the two most symptomatic joints in men. In women, DIP (9.4%), PIP (7.3%) and thumb base (5.7%) were the most symptomatic. Osteoarthritis was more likely to cluster by row than by ray and occurred in a remarkably symmetrical pattern, especially in women [41]. In contrast to the Framingham study, the Rotterdam study demonstrated that the strongest association of right hand pain was with thumb base (odds ratio [OR] 1.7) followed by PIP (OR 1.4). Radiographic DIP OA was not associated with hand pain (OR 1.1) [40]. In the NHANES III study, the overall symptomatic hand OA prevalence was 8% (8.9% female; 6.7% male) in American adults 60 years of age and older and it significantly increased with age [42].

**Prevalence of knee osteoarthritis**

Depending on the study, overall prevalence of radiographic knee OA in American subjects 45 years of age and older varies between 19.2% and 27.8%, with women more predisposed than men. Similarly, in the largest European survey, the Zoetermeer Community Survey in the Netherlands, the prevalence of radiographic knee OA was higher in women than in men of 45 years and older with 22,800 compared to 14,100 out of 100,000 citizens [43]. A more global perspective in knee and hip OA prevalence has also been reported by the World Health Organization [44]. In NHANES III, the overall prevalence of knee OA worldwide increased to 37.4% in subjects 60 years of age and older. It is likely that the protocol employed for NHANES III knee examination biased the prevalence estimates to be lower than the true population values, since only a single anterior/posterior non-weight-bearing radiograph for each knee was examined [38]. As did the first national Health and Nutrition Examination Survey (HANES I) [45], NHANES III also reported that the prevalence of radiographic knee OA was significantly higher in non-Hispanic African Americans than in non-Hispanic Caucasians or Mexican Americans (52.4%, 36.2%, and 37.6%, respectively) [38]. More
recent studies have demonstrated statistically significant greater severity of knee OA in African Americans than in Caucasians (adjusted cumulative OR of 2.08; 95% confidence interval [CI]: 1.19–3.64, for men and 1.56; 95% CI: 1.06–2.29, for women) [46]. This study evaluated not only the tibiofemoral but also the patellofemoral compartment and demonstrated increased tri-compartmental disease in African Americans. In fact, care must be taken when evaluating radiographic prevalence of knee OA. Indeed, most studies evaluated the tibiofemoral compartment, thus underestimating the tibiopatellar compartment, which can be a major source of radiographic and clinical OA, particularly in a younger population [47].

Classically, knee pain and radiographic OA changes have been discordant [48]. Some studies attribute this discrepancy to the radiographic view chosen to define radiographic OA [49]. Other explanations may be the variation in populations analyzed, the definition of pain in the various studies, and/or that pain can be experienced without visible radiographic alterations. However, other reports estimate that 40% to 80% of subjects with radiographic knee OA are symptomatic [50] and a recent study on two cohorts reported a strong association between radiographic features of OA and knee pain [51]. In the Framingham study, the prevalence of clinical knee OA was 4.9% and 6.7% for subjects older than 26 and 45 years, respectively [36]. In the Johnston County OA project, the prevalence of clinical knee OA was much higher than in the Framingham study, with 16.7% for adults over 45 [37]. NHANES III estimated a 12.1% prevalence of symptomatic knee OA in subjects over 60, which was similar to the Rotterdam study [52]. The remarkably higher prevalence of symptomatic knee OA in the Johnston study [37] could be due to multiple factors. Johnston County, North Carolina, United States, has a high prevalence of sociodemographic subgroups at high risk for OA, with 20% African Americans. As recently demonstrated, both men and women of African American origin are more likely to have osteophytes [46]. Since the presence of osteophytes seems to be predictive of symptoms, at least in the knee, this could explain the higher prevalence of clinical OA in the Johnston study [53]. Recently, the Clearwater Osteoarthritis Study [54] reported that subjects with radiographic knee OA with an elevated body mass index (BMI) had a greater likelihood of knee pain than those with normal BMI, and this rose with each successive elevated BMI category [55]. This concurs with two prior studies [56, 57], but contrasts with a third [58]. A more precise and homogeneous definition of radiographic and symptomatic knee OA between studies, as well as a more sensitive method
for knee assessment, such as MRI, are needed to further clarify the prevalence of and risk factors for this disease. In this line of thought, a recent systematic review of the association between MRI findings (cartilage defects, bone marrow lesions (BML), osteophytes, meniscal lesions, effusion/synovitis, ligament abnormalities, subchondral cysts and bone attrition) and pain in patients with knee OA revealed that BML and effusion/synovitis may indicate the origin of pain in knee OA [59].

Prevalence of hip osteoarthritis

In the Johnston County OA project, the prevalence of radiographic hip OA based on KL grade ≥ 2 was 27% in adults 45 years of age and older [39]. As with the other joints, the prevalence increased with age (from 21% at 45-54 years to 43% over 75 years) and was slightly higher in women than men (30% vs 25%). Although some previous studies demonstrated low prevalence of hip OA in African populations [60], this does not seem to apply to Americans of African descent, at least not in the Johnston County OA project or the NHANES I cohort [61, 62]. In both of these studies, no differences were found between the prevalence of hip OA between African Americans and Caucasians. However, the hips of African American men and women had an increased frequency and severity of superior joint space narrowing compared with the hips of Caucasian men and women [32]. In the NHANES I study, the overall prevalence of hip OA in people 55-74 years old was only 3.1%, also based on KL grade ≥ 2. As in the Johnston County OA project, the prevalence increased with age, as indicated by the significantly higher OR in the older group (70-74 years: OR 2.38; 95% CI: 1.15-4.92) compared to the younger group (60-65 years: OR 1.30; 95% CI: 0.6-2.81). In another community-based study in the United States of nearly 5,000 women aged 65 and older, the prevalence was found to be 7.2% [63].

The two first population-based prevalence estimations of symptomatic hip OA were NHANES I (1971-1975) and NHANES III (1988-1994). In NHANES I, the overall prevalence of symptomatic hip OA in adults (55-74 years) was 0.7% and like the radiographic prevalence, the rates increased with age and were similar between Caucasians and African Americans and between sexes [61]. NHANES III reported an increase in overall hip pain prevalence since the previous study, with 14.3% of older adults (≥ 60 years) with significant hip pain [64]. As in the NHANES I study, women were more affected, but age did not influence hip pain, at least in males. Caucasian women had 16% prevalence compared with 14.8% in African
American women, and men had 12.4% prevalence with similar rates for both races. The higher prevalence of hip pain in NHANES III may be related to non-articular sources of pain in older adults or with increased incidence of hip OA [62]. Finally, in the Johnston County OA project, 9.2% of adults were symptomatic (9.3% female, 8.7% male) [39]. Like NHANES I, African Americans were not less affected by symptomatic hip OA than Caucasians.

**Established risk factors for osteoarthritis**

There are numerous studies on risk factors for OA. Classically, they can be divided into two broad categories: systemic factors, which are associated with the development of OA, and local factors, which affect biomechanical loading of the joint [65] (Figure 1). Since the pathophysiology of OA is multifactorial, both systemic and local factors may influence the outcome of OA by increasing the susceptibility of a joint to develop OA upon utilization.

**Systemic and local factors in the pathophysiology of osteoarthritis**

![Systemic and local factors in the pathophysiology of osteoarthritis](image)

**Figure 1.** Pathogenesis of OA with systemic and local risk factors. Adapted from Figure 1 of Dieppe P. The classification and diagnosis of osteoarthritis. In: Kuttner K, Goldberg V, eds. Osteoarthritic Disorders. Rosemont, IL: American Academy of Orthopaedic Surgeons; 1995:7.
Systemic risk factors

Age

Even though aging is not sufficient for the development of OA, it is still the strongest risk factor for OA in all joints [66, 67]. However, the mechanism by which age increases the susceptibility to joint degeneration is still largely unknown. Age-related changes in articular cartilage likely play a role. They could be related, among other things, to an alteration within the collagen network crosslinking resulting from the advanced glycation end products [68], a decreased response of chondrocytes to repair stimuli [69] and/or altered levels of cartilage oligomeric protein and hyaluronic acid [70]. Yet, other less cartilage-oriented mechanisms could also be implicated, such as decreased proprioception and muscle strength or unstable articulation with aging [71, 72]. Nevertheless, it appears that the increased prevalence of OA with aging is multifactorial and includes the abovementioned mechanisms as well as, very importantly, increased susceptibility to other OA risk factors [34, 73].

Gender and estrogens

Women are more susceptible than men to OA as well as to higher disease severity [74]. The significant increase in OA prevalence in women around the time of menopause has led to multiple investigations of the hormonal implication in the pathophysiology of OA. In contrast to other tissues (such as endometrium, breast and brain), joint tissues were traditionally thought to be non-responsive to estrogen or to its deficit. However, although data are conflicting [75], there is now increasing evidence that estrogen influences the activity of joint tissues through complex molecular pathways that act at multiple levels [76]. The Framingham study concluded that estrogen intake in women had a modest but non-significant protective effect on both radiographic OA (OR 0.71; 95% CI: 0.42-1.20) and severe radiographic OA (OR 0.66; 95% CI: 0.33-1.32) [77]. On the other hand, it was also reported that women on estrogen replacement therapy were less likely to require total knee or hip replacement [78, 79]. The benefit seemed to increase with long term use. Indeed, those who had taken estrogen for 10 years or longer had a greater decrease in the risk for hip OA; however, there was no significant reduction in disease symptoms [79, 80]. Moreover, two reviews on the subject by the same group [81, 82] reported that data on endogenous hormones, age at menarche/menopause, and duration of the fertile period, etc. in hand, hip and knee OA, point to no relationship between OA and female
hormonal aspects, or remain conflicting. Nonetheless, there appears to be some evidence that unopposed estrogen use has a protective effect on hip OA. It thus seems that further research is needed to clarify the complex role of estrogen in the pathophysiology of OA.

Race

Numerous studies support the role of ethnicity in the development of OA based on variations among racial and ethnic groups [34]. For example, both hip [83] and hand OA [84] were found to be rare among Chinese in the Beijing Osteoarthritis Study compared to Caucasians in the NHANES I study (80%-90% less frequent hip OA) and Framingham study (about 35% less frequent hand OA) respectively. However, both radiographic and symptomatic knee OA were increased by about 45% in Chinese women compared to the Framingham study [85]. Zhang et al. [86] reported that the higher prevalence of knee OA in Chinese women could be explained by increased manual labour and squatting. As discussed in the previous section, the prevalence of hip OA was similar between African American and Caucasian women, despite a previous report indicating a lower prevalence [60].

Genetics

It has been suspected for nearly seven decades that genetics have a strong influence on the incidence of OA [87]. Osteoarthritis is a multifactorial and polygenic late-onset disease in which environmental factors are key modulators of gene expression [88]. Family studies from the early 1960s reported that first-degree relatives were twice as likely to have radiographic generalized OA [89]. More recently, multiple twin and family studies have reported hand, hip and knee OA. Spector et al. [90] evaluated the genetic influences on OA in twin women and demonstrated a clear genetic impact for radiographic hand and knee OA, with an estimable heritable component ranging from 39-65% with monozygotic twins having a concordance rate nearly 70% higher than dizygotic. Similarly, in another radiographic hip OA study, the same group reported that about 60% of overall hip OA was hereditary in women [91]. These findings from twins are now corroborated with large population-based family studies with closely matched estimates of heritability. For example, the Rotterdam study estimated 56% heritability in hand OA [92]. In a population with clinical and radiographic hand OA and their siblings, the presence of osteophytes was the most sensitive biomarker
of hand OA heritability, with the first interphalangeal joint having 70% heritability in Caucasians [93].

An increasingly popular approach to investigating the genetic etiology of OA is genetic association studies (GAS) [94]. In order to explore each gene variant in OA, Zintzaras et al. [95] analyzed the data from 327 GAS and catalogued them in Cumulative Meta-Analysis of Genetic Association Studies CUMAGAS-OSTEO, a web-based information system (http://biomath.med.uth.gr). They reported that 19 gene variants significantly increased the risk for OA by 30% or more, with GDF5 and LRCH1 being the most important variants. Another means to evaluate the influence of genetics in OA is with linkage analysis. Genetic linkage occurs when a locus involving OA and alleles of a nearby marker are inherited together. A recent meta-analysis summarized linkage of OA susceptibility genes to regions 7q34–7q36.3, 11p12–11q13.4, 6p21.1–6q15, 2q31.1–2q34 and 15q21.3–15q26.1 [96]. Valdes et al. [97] reported that genetic pathways involving the bone morphogenic protein and the wingless signalling are also implicated. Moreover, it is becoming increasingly evident that synovitis and inflammation are also involved in the etiology of OA, and that inflammatory molecules including those related to the metabolism of cytokines, prostaglandins, and arachidonic acid are associated with susceptibility to OA.

**Nutritional factors**

Nutritional factors have long been the subject of considerable interest in OA even though the results are conflicting. One of the most important factors for bone development and remodelling is vitamin D. Since vitamin D influences bone quality, it has long been suspected that its status could have an effect on the risk of the development or progression of OA [98]. In the Framingham study, adults in the middle and highest tertiles of 25-OH-D intake had a 3-fold reduction in risk for radiographic knee OA compared to those with lower intake [99]. In the more recent Rotterdam study, it was also demonstrated that a low dietary vitamin D intake increases the risk for knee OA progression (12.6% in the lowest tertile vs 5.1% in the highest tertile), particularly in subjects with low baseline bone mineral density [98]. Another study also demonstrated that sunlight exposure and serum 25-OH-D levels are both associated with decreased knee cartilage loss (assessed by radiograph or magnetic resonance imaging) [100]. Moreover, the Study of Osteoporotic Fractures reported that women in the middle or lowest tertile of 25-OH-D had a 3-fold increase in incidence of hip OA [101]. However, a study on bone turnover, vitamin D, and calcium regulation in Caucasian twin pairs (66 MZ and 163 DZ) discordant for knee OA, found no difference in
these markers after adjusting for age and BMI [102]. In a review of two longitudinal studies, the Framingham Osteoarthritis Study (Framingham Offspring cohort) and the Boston Osteoarthritis of the Knee Study, it is concluded that vitamin D status is unrelated to the risk of joint space or cartilage loss in knee OA [103, 104].

McAlindon et al. [105] were the first to report that high intake of β-carotene and vitamin C reduced the risk of progression of radiographic knee OA; however, these products had no effect on knee OA incidence. In a well designed two-year randomized placebo controlled study, Wluka et al. [106] concluded that supplementary vitamin E does not affect the loss of cartilage volume in knee OA, corroborating a study on symptomatic relief of knee OA [107].

Multiple other nutritional factors such as ascorbic acid, other vitamins, minerals, fatty acids, flavonoids and ginger have been studied, but also with variable results. Even though some studies suggest a correlation between these factors and OA or symptom improvement, the role of nutrition in slowing down the disease progression remains to be thoroughly evaluated.

**Bone density**

As is now well known, OA is certainly not limited to cartilage degeneration, but involves all components (tissues) of the joint [108]. Literature in recent years has shown increased interest in the implication of bone density and the subchondral bone in the development, or even the initiation, of OA. The bone tissue involvement at the molecular level is discussed in detail in Chapter 5 - *Subchondral bone involvement in the pathophysiology of osteoarthritis*.

**Local risk factors**

The systemic factors previously discussed are key modulators of OA susceptibility but they are frequently associated with local biomechanical and biochemical factors. Following is a review of the biomechanical factors; the biochemical factors are extensively discussed in other chapters.

**Biomechanical factors**

Knee OA progression is found to be often driven by biomechanical forces. The subsequent pathological response of tissues to such forces leads to structural deterioration, symptoms, and reduced knee function. Tetsworth and Paley estimated that as little as 5° of genu varum results in about 80%
higher compressive force on the medial knee compartment [109]. Sharma et al. [54] demonstrated that varus of 5° or more was associated with a 4-fold increased risk of medial knee OA progression, and valgus deformation with a 5-fold increase in lateral progression, and that the severity of the malalignment predicted the decline in physical function at 18 months. Chang et al. [110] subsequently evaluated thrust during ambulation and the progression of knee OA and reported that varus thrust increased 4-fold medial knee OA progression (and varus alignment increased it 3-fold). Using the Osteoarthritis Initiative cohort of knee OA, a recent study demonstrated that African Americans with knee OA had about half the odds of varus thrust compared to Caucasians, and about twice the odds of valgus thrust, adding new insight to the difference in pattern of OA involvement between these groups [111]. It is also well known that concomitant risk factors such as obesity play a role in the impact of the biomechanics in OA development [112]. For example, the genu varum malalignment, having a high bone mass index led to increased OA severity, which is not the case with genu valgum [113]. However, even with strong evidence that malalignment is a risk factor for OA progression [54, 114], data from the Framingham study did not establish a relationship between malalignment and OA incidence [115, 116].

**Muscle strength**

In contrast to high bone mass index or malalignment, muscle strength is a more easily modified risk factor for OA. However, data on the association between the incidence and progression of knee OA and lower quadriceps muscle strength are variable. Some report that 18% lower knee extensor strength in women is associated with a higher incidence of OA [117], while others showed that moderate or high quadriceps strength in women significantly reduced, by about 60%, the risk of hip or knee OA [118]. Moreover, in the largest study to date in this field of research, Segal et al. [119] reported that quadriceps weakness predicted risk for knee joint space narrowing in women but not in men. This study demonstrated that women in the lowest tertile of quadriceps strength had nearly 70% increased risk for whole knee joint space narrowing and tibiofemoral joint space narrowing. The discrepancies between men and women were explained by greater strength in men, thus protecting them against reaching a threshold under which strength becomes a risk factor for OA [120]. However, in another recent longitudinal study by Segal et al. [121], thigh muscle strength failed to predict radiographic knee OA incidence, but demonstrated that higher extensor strength nearly halved the incidence of symptomatic OA in both sexes. Several other studies found no association between muscle weakness
and worsening of OA in women [122, 120]. In contrast, a study by Sharma et al. [72] reported that in the context of malalignment and laxity, greater muscle strength may actually increase the risk for OA progression. In this context, Chaisson et al. [123] reported that men with hand OA with greater grip strength in the Framingham cohort were at increased risk for developing carpometacarpal, metacarpophalangeal and PIP OA. The discrepancies between these studies merit further evaluation since they could have a major impact on future OA management. For example, several studies have shown that quadriceps strengthening exercises may improve joint pain in subjects with knee OA [124, 125].

**Exercise**

Despite the common misconception that exercise is deleterious to one’s joints, there is no evidence to support this notion in the absence of joint injury [126]. In addition to its various well recognized health benefits, exercise is also beneficial to joint tissues [127]. In evaluating the risk of developing OA from sports participation, it is important to discriminate recreational and professional sports participants, since the latter are at higher risk for injury associated with subsequent OA development, especially those in sports involving high impact and repetitive movement [128]. Initial studies on recreational weight-bearing exercise or jogging reported no association between moderate exercise and joint degeneration in the absence of other factors [129-132]. However, some population-based studies have reported an increase in knee and hip OA with higher exposure to sporting activities. Vingard et al. [133, 134] reported a relative risk of 4.5 for men and 2.3 for women of developing hip OA in the higher activity group. Another study demonstrated that male runners below the age of 50 who ran more than 20 miles per week were at greater risk for developing OA (OR 2.4; 95% CI: 1.5-3.9) [135]. Sports requiring high torsional loading, such as in the elbows of professional baseball players or elite javelin throwers, are particularly associated with OA [128, 136] and elite javelin throwers and high jumpers are about three times more at risk for hip OA than non-athletes [126]. Some studies have also demonstrated a prevalence of knee OA in former elite middle and long distance runners [137]; however, this is controversial, since others found no increased prevalence of OA in such groups. It would thus seem that elite athletes performing high impact, repetitive or torsional stress activities are at risk for developing OA but probably secondary to the greater risk of concomitant injury than the activity itself [128]. Indeed, since the joint can be considered a complex organ, the global effect of physical activity on the joint is multifactorial and every aspect including bone density, muscle
strength, proprioception, and risk of injury, must be evaluated to predict the net effect.

**Joint injury**

Although recreational physical activity and sports alone do not appear to be risk factors for developing OA, it has been clearly demonstrated that injuries can counteract the beneficial aspects of sports and lead to secondary OA. A variety of joint injuries are clearly related to the incidence of OA, particularly in the knee, but nearly all joints can be affected. A recent review of sports injuries reported that approximately 15% of sports related injuries in children and teenagers were associated with growth disturbance [138]. In adults, Felson et al. [139] reported that knee injury is the leading modifiable risk factor for OA in men and the second in women (after obesity). In soccer players, the prevalence of knee OA is higher (26%) than in runners (14%), which can be explained by increased risk of injury in the former group [140]. The most frequently reported injuries are anterior cruciate ligament (ACL) injuries and meniscal tears. As reported by Keays et al. [141], the incidence of OA after ACL reconstruction is alarmingly high, with reports as high as 50% at 6 years. In this study, the highest predictive factor for subsequent knee OA after ACL repair was meniscectomy and chondral damage. Moreover, a recent meta-analysis of knee OA after ACL injury indicated that the prevalence was only between 0%-13% for subjects with isolated ACL injury, but increased to 21%-48% with additional meniscal tear [142]. In their 21-year follow-up study of knee OA after meniscectomy, Roos et al. [143] reported mild radiographic changes in 71% and moderate (≥ KL 2) in 28% of the knees, nearly four to seven times more than healthy control knees. The relative risk for the presence of the more advanced tibiofemoral radiographic changes was 14.0 (95% CI: 3.5-121.2). Even in the 1940s, it was speculated that the increased risk for OA after meniscectomy was probably caused by the increased mechanical stress on the cartilage and subchondral bone due to changes in the knee biomechanics [144]. Unfortunately, to date, ACL reconstruction and meniscectomy cannot completely restore the joint and prevent subsequent OA development.

**Obesity**

Obesity is the strongest modifiable risk factor for OA, possibly due to the high mechanical stresses imposed on the joint. Indeed, it is well demonstrated that OA prevalence in knee [67, 145] and possibly hip [146] and hand OA [147] are increased in overweight people. In the Framingham study, the BMI
at study entry predicted the presence of radiographic knee OA 36 years later [148]. In this context, another study using the Framingham data also demonstrated that a reduction of about 5 kg in women resulted in a 50% reduction in the development of symptomatic knee OA [149] and a meta-analysis of randomized controlled trials reported that patients who reduced their body weight by at least 5% within a 20-week period experienced symptomatic relief of knee OA [150].

Interestingly, since obesity is also a risk factor for non-weight-bearing joints such as the hand [147], which cannot be explained by mechanical factors, an increasing number of studies are focusing their attention on evaluating the presence of possible obesity-related systemic factors in the pathogenesis of OA. Hu et al. [151] recently reviewed the adipokines, one of the emerging classes of molecules implicated in the systemic factors of OA. Discovered by Zhang and Friedman [152] with the cloning of leptin, adipokines or white adipose tissue cytokines, can act via autocrine and paracrine pathways which could explain the systemic effect of obesity in OA and rheumatoid arthritis [153]. To date, the major adipokines implicated in OA are leptin, adiponectin, resistin and visfatin. Although their roles still need to be clarified, it seems that adipokines may soon be pivotal to the diagnosis and prognosis of, and pharmacological approaches to, rheumatoid arthritis and OA [151, 153].

**Occupation**

Studies of occupational groups have demonstrated a clear relationship with the incidence of OA for over 60 years. Indeed, in 1952, Kellgren and Lawrence [154] demonstrated that in adults between 40 and 50, miners showed significantly higher prevalence of knee OA than both manual and office workers. Although OA is a multifactorial disease, there is current evidence that occupational activities requiring repetitive use can be a risk factor for OA. For example, men working in agriculture had a 2.3 (95% CI: 2.1-2.5) increase in prevalence of OA in the overstimulated joint compared to other occupations [155]. In a systematic review, Lieverse et al. [156] also found moderate evidence of an association between previous heavy physical workload and hip OA, with an odds ratio of nearly 3. Multiple other studies have demonstrated that heavy physical work involving knee bending or squatting is associated with a higher prevalence of knee OA. More recently, a study from the Johnston County Osteoarthritis Project confirmed an association between physically demanding occupational tasks (lifting over 10 pounds, crawling, heavy work while standing) and both symptomatic knee and hip OA (OR 1.4-2.1), but failed to demonstrate radiographic changes
The absence of radiographic progression could be explained, at least in part, by multiple factors such as the lack of sensitivity of X-rays. Indeed, an MRI study in women recently demonstrated that those physically demanding occupations affect patellar but not tibial cartilage, which is not well evaluated by X-rays [158].

**Conclusion**

Osteoarthritis is the most common form of arthritis and is associated with an alarmingly increasing socioeconomic impact. Even though it is one of the oldest diseases affecting humankind, the pathophysiology of OA is still evolving, from being viewed as cartilage-limited to a multifactorial disease affecting the whole joint. The prevalence of OA varies by site, age, gender and ethnicity. Moreover, an intricate relationship between local and systemic factors modulates the radiological and clinical presentation of OA. Evolving radiological and clinical definitions and a better control and understanding of the various risk factors will improve our knowledge of OA and ultimately lead to new pharmacological and non-pharmacological therapies.

**References**

Epidemiology of osteoarthritis

56. Marks, R. 2007, Obesity (Silver Spring), 15, 1867.
Epidemiology of osteoarthritis


