Osteoarthritis

Osteoartrite

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ABSTRACT

Osteoarthritis is nowadays one of the most frequent chronic diseases and, with the increase in life expectancy, both its prevalence and incidence is expected to rise. This condition is progressive and leads to functional decline and loss in quality of life, with important health care and society costs. A review of relevant and recent literature on osteoarthritis was performed in PubMed. The purpose of this study is to understand important aspects about osteoarthritis estimates, burden of disease, pathophysiology, risk factors, diagnosis and treatment.

Keywords: Osteoarthritis/epidemiology; Osteoarthritis/physiopathology; Risk Factors; Osteoarthritis/diagnosis; Osteoarthritis/therapy; Portugal.

RESUMO

A osteoartrose é uma das doenças crónicas mais frequentes na atualidade e, com o aumento da esperança de vida, quer a sua prevalência quer a sua incidência tendem a aumentar. Esta patologia é progressiva e condiciona perda funcional e de qualidade de vida, com importante impacto em termos sociais e de consumo de recursos de saúde. Foi efectuada uma pesquisa na PubMed de literatura relevante e recente acerca da osteoartrose. O objectivo deste estudo é descrever aspectos relacionados com as estimativas da doença, custos associados, patofisiologia, factores de risco, diagnóstico e tratamento da osteoartrose.

Palavras-chave: Osteoartrose/epidemiologia; Osteoartrose/patofisiologia; Factores de Risco; Osteoartrose/diagnóstico; Osteoartrose/tratamento; Portugal.

Osteoarthritis: definition and diagnosis

Osteoarthritis is the most frequent musculoskeletal disease and leads to functional decline and loss in quality of life. Clinically, the condition is characterized by joint pain, tenderness, crepitus, stiffness and limitation of movement with occasional effusion and variable degrees of local inflammation.1 The pain in osteoarthritis is frequently activity-related, with pain coming on generally in specific activities that induce it; constant pain frequently becomes a feature later in the disease.2 Pain in osteoarthritis is not simply attributable to the structural changes in the affected joint, but the result of interplay between structural change, peripheral and central pain processing mechanisms.3

There is also the emerging idea about the importance of understanding both biological and psychosocial factors in the assessment and treatment of osteoarthritis. A recent study identified that osteoarthritic related pain needs to be considered and interpreted in accordance with the patient’s psychological status.4

However, pain is not the only consequence of osteoarthritis experienced by patients. Pain is linked with function, with physical movements triggering pain, while pain, in turn, causes limitations in physical function.5 Joint stiffness particularly in the morning is also frequent; sensation of instability or buckling and also an audible and palpable ‘cracking’ or ‘crunching’ over a joint during its active or passive movement are also common specially in later stages.3 This can be caused by pain, effusion, capsular contractures, muscle spasm or weakness, intra-articular loose bodies, mechanical constraints and joint deformity/ misalignment.5

Functional disability is another key element in osteoarthritis. It is frequently associated with articular limitation, stiffness and crepitus.6 Osteoarthritis causes changes in mobility and function; Patients frequently experience physical limitations, difficulties with personal care, work ability and even problems with maintaining their household.6,7

In a clinical setting, osteoarthritis diagnosis is normally made using established methods such as radiographic changes and clinical guidelines, which are used as a ‘diagnostic reference’.8 Evidence-based recommendations were defined by the European League Against Rheumatism and the American College of Rheumatology. Although the pathophysiological changes of osteoarthritis are well described, differences between joint sites should be considered to improve case ascertainment since differences can be expected in the way articular changes produce signs and symptoms within different joints.9,11
The American College of Rheumatology guidelines for hand osteoarthritis include the presence of hand pain, aching, or stiffness and 3 out of 4 of the following features (hard tissue enlargement of 2 or more of 10 selected joints; hard tissue enlargement of 2 or more distal interphalangeal joints; fewer than 3 swollen metacarpophalangeal joints; or deformity of at least 1 out of 10 selected joints).12 For hip osteoarthritis, the presence of hip pain and at least 2 of the following 3 features: erythrocyte sedimentary rate <20 mm/hour; radiographic femoral or acetabular osteophytes; or radiographic joint space narrowing.13 For the knee, there are 3 possible diagnosis recommendations (clinical, clinical plus laboratory and clinical plus radiographic). Clinical plus radiographic requires: the presence of osteophytes plus knee pain and at least 1 out of 3 of the following aspects: age > 50 years, stiffness < 30 minutes and crepitus.14

The European League Against Rheumatism evidence-based recommendations for the diagnosis of osteoarthritis state that, although specific aspects are defined for each joint, a confident diagnosis may be made according to symptoms (pain, stiffness and functional limitation) and signs on examination (crepitus, restricted movement and bony enlargement/deformation); plain radiography provides the morphological assessment of osteo-articular changes (but may be not necessary in some cases) and occasionally other investigations may be considered for the diagnosis of atypical situations or to exclude other possible conditions.15-17

Biomarkers provide useful diagnostic information by detecting cartilage degradation in osteoarthritis, reflecting disease-relevant biological activity and predicting the course of disease progression.18 But, although some biological markers of joint metabolism might be significantly increased in a group of patients with osteoarthritis, these markers cannot be used as diagnostic tests in individual patients.19,20 Although several studies are underway, currently there are no reliable, quantifiable and easily measured biomarkers that provide an earlier diagnosis of osteoarthritis, information on the prognostic of disease and which can monitor responses to therapeutic modalities.18

Osteoarthritis Epidemiology

Osteoarthritis is the most common musculoskeletal disorder worldwide21 and an increasingly important public health concern.22 Epidemiologic characterization of osteoarthritis is required as a basis for decisions on health prevention and treatment programs.23

It is known that prior to age 40, the incidence is lower and most frequently is secondary, commonly due to trauma.24 The prevalence increases between 40 and 60 years, and there is a linear increase in the prevalence in later ages.5 Worldwide disease estimates show that that 9.6% of men and 18% of women of 60 or older probably have symptomatic osteoarthritis.24

The estimates of osteoarthritis seem to change according to the case definition used but also by the specific joint(s) under study and the characteristics of the studied population.23,25,26 Results from a systematic review27 presented in knee, prevalences that ranged from 6.3% in Greece28 to 68.4% in the UK;29 in hip, from 0.9% in Greece28 to 23% in Croatia,30 in hand from 2% in Greece28 to 77.1% in Israel.31

In Portugal, the Instituto Nacional Dr. Ricardo Jorge, in a report on the most prevalent chronic diseases, identified that 24% of the participants reported suffering from some form of rheumatic disease.32 Particularly, as far as osteoarthritis is concerned, general data presented by the Liga Portuguesa Contra as Doenças Reumáticas estimates that probably 6% of the Portuguese population has the disease;33 the Direcção Geral da Saúde, in a report from 2003, described that the prevalence of osteoarthritis was approximately 3.8% in knee and 1.3% in hip.34 Also in Portugal, Costa et al35 study estimated that the self-reported prevalence of osteoarthritis in adults above 18 years old, in the knee was 11.1% [95% Confidence Interval (95% CI) CI: 9.4-13.1], [5.9% (95% CI: 3.9-8.6) in men and 14.2% (95% CI: 11.8-16.9) in women] and for the hip 5.5% (95% CI: 4.3-7.0), [2.2% (95% CI: 1.1-4.2) in men and 7.4% (95% CI: 5.7-9.5) in women]. Other important data is presented by the Observatório Nacional das Doenças Reumáticas (ONDOR) that estimated radiographic knee osteoarthritis, in subjects older than 40 years, was 56.9% [95% CI: 51.6-62.1] in men and 57.7% (95% CI: 63.3-62.0) in women; radiographic hip osteoarthritis was 54.8% (95% CI: 38.7-70.2) in men and 24.5% (95% CI: 20.4-28.9) in women; symptomatic disease estimates were 6.0% (95% CI: 3.7-9.2) in men and 15.8% (95% CI: 12.6-19.5) in women for knee; 2.4% (95% CI: 1.0-4.1) in women, for hip.36 (Table 1).

There is relatively little information worldwide on the incidence of osteoarthritis compared to prevalence data.37 For example, in the USA, the age and sex standardized incidence rates for symptomatic osteoarthritis were 0.24 person-years for the knee, 0.09 person-years for hip and 0.1 person-years for the hand.38 Grotle et al,39 in Norway, found a cumulative incidence of 7.3% (95% CI: 5.7-9.0) in the knee, 5.8% (95% CI: 4.3-7.3) in hip and 5.6% (95% CI: 4.2-7.1) in hand joints. To our knowledge, in Portugal no published data is available for osteoarthritis incidence.

Burden of Disease

Estimates of osteoarthritis burden need to take into consideration economic, social and/or psychological costs or losses to the patient, family and/or society.40 Although osteoarthritis is considered both a common and highly burdensome disease, few studies worldwide have focused on this issue.41 Moreover, the comparability across studies is quite limited, highlighting the importance of standardized methodologies in cost-of-illness studies.40

Information on the impact and overall costs of this rheumatic disease involves direct, indirect and intangible costs measurement. Direct costs are defined as the resources used in research, prevention, detection, and treatment of disease.32 They comprise medical and non-
Increased government support payments, workforce participation, lost income, taxation revenue, and as a result of medical management of the disease but rather in Canada, $1271 in Italy, and $345 in France.

In a systematic review including 10 studies, after evaluating the burden of osteoarthritis, since this pathology is no published data on specific direct and indirect costs, only 5 studies reported data: the highest indirect costs were $9847 per patient, per year, in Canada and the lowest were $864 in Hong Kong. More recently, in Spain, Loza et al. found that the annual cost per patient was 1502 €; the direct costs represented 86% and the indirect 14% of the total expenditure.

Although osteoarthritis represents an important burden for individuals and health care systems, in Portugal there is no published data on specific direct and indirect costs, to allow comparisons. The Sociedade Portuguesa de Reumatologia estimates that in 1997 all rheumatic diseases were the first cause for a medical visit (23% of total cases), the first cause for early retirement and caused disability in 98% of patients with rheumatic disease.

Apart from the direct and indirect costs cited, there are also intangible costs such as pain, suffering and changes in patients’ quality of life. These are key issues to evaluate the burden of osteoarthritis, since this pathology can profoundly affect many aspects of the daily life of the individual, including quality of life, mental well-being and emotional relationships. However, this kind of cost is even harder to evaluate and frequently not considered as cost-of-disease.

**Pathophysiology**

Osteoarthritis is an irreversible disease, which leads to pain and loss of joint function. The main characteristic of the disease is the loss of articular cartilage and subchondral bone sclerosis. Histologically, the disease is characterized by early fragmentation of the cartilage surface, cloning of chondrocytes, vertical clefts in the cartilage, variable crystal deposition, remodelling, and eventual violation of the tidemark by blood vessels. But the degenerative disease process not only affects the articular cartilage but also involves the entire joint, including the subchondral bone, ligaments, capsule, synovial membrane and peri-articular muscles. Bone remodeling and attrition occur relatively early in the disease process caused by fibrocartilage degeneration, chondro-osteophytes, protrusions, subsynovial inflammatory cells and synovium cell hyperplasia; activated synovium secretes excess synovial fluid, leading to capsular swelling. This swelling, through a spinal reflex, inhibits complete activation of muscles bridging the joint (arthrogenous inhibition) and this, combined with lack of use, leads to muscle weakness and atrophy.

In general, osteoarthritis may be a slow but efficient repair process that often compensates an initial trauma/metabolic/systemic change, resulting in a structurally altered but symptom-free joint. In some people, however, either because of overwhelming insult or compromised repair potential, the process cannot be compensated, resulting in continuing tissue damage and eventual presentation with symptoms and ‘joint failure.’

Osteoarthritis is a complex disease which, through a combination of structural, mechanical, and biological pathways, causes degeneration of the joint components. It has a multi-factorial etiology and can be considered the product of interplay between systemic and local factors.

**Risk Factors**

The relative importance of risk factors may vary for different joints and according to the stages of the disease. It is also difficult to make a distinction between single and clustered risk factors associated with the disease development or progression. Genetic and genomic approaches have tried to find novel biological pathways involved in osteoarthritis. Through twin studies it has been well-established that osteoarthritis and its endophenotypes are, to a large extent genetically determined, but the underlying genetic variants are mostly unknown. The genetic architecture is similar.
to other complex diseases with contributions of several or even perhaps hundreds of genes, most of them having small effects and a few having large effects. 54,55

Genetic association approaches have shown to be fruitful in identifying underlying genetic factors. 2,23,54,56 The most consistently confirmed genetic association is for a gene coding secreted frizzled-related protein-3 (usually called FRZB), an association reported especially in relation to the risk of hip osteoarthritis in women. 55

It is also important to remember that the early onset of osteoarthritis can be distinguished, which usually represents a monogenic Mendelian disease type and can be mapped by linkage analysis in families, or nowadays by exome sequencing of affected subjects. On the other hand, in late onset, which represents the most common form of osteoarthritis with a usual higher age of onset (> 60 years), genetic association approaches have been shown to be fruitful in identifying underlying genetic factors. 2,23,54,56

Age is the strongest predictor of osteoarthritis development. 57 The vulnerabilities of a joint that occur as part of the aging process make it susceptible to disease. 48 Age-related morphologic changes in articular cartilage are probably due to a decrease in chondrocytes’ ability to maintain and repair the tissue; chondrocytes undergo age-related decreases in mitotic and synthetic activity, exhibit decreased responsiveness to anabolic growth factors, and synthesize smaller and less uniform large aggregating proteoglycans and fewer functional link proteins. 58

Diminished capacity for cartilage repair, hormonal changes and the cumulative effects of environmental exposures are also possible age-related mechanisms. 9 Several studies support this associations: for example, incident knee osteoarthropathies were found to increase by 20% per 5-year age increase. 56 Andrianakos et al 60 found age > 50 was a risk factor for knee, hip and hand osteoarthritis.

Independently of age, osteoarthritis occurrence differs by gender, with females presenting higher risk of developing the disease than men. Gender differences seem to be less marked in older ages. 55 The reason for these sex differences are unclear, but some explanations are plausible: articular chondrocytes possess functional estrogen receptors, and there is evidence that estrogen can up-regulate proteoglycans synthesis. 58 In support of a role for estrogens in osteoarthritis, there are studies indicating that estrogen replacement therapy may reduce the incidence of the disease 61 although evidence is not always consistent. 62,63 For example, as far as progression is concerned, one 4-year follow-up study showed no effect of estrogen plus progestin versus placebo on symptoms or disability in postmenopausal women. 64

Among the modifiable risk factors, overweight and obesity are recognised as risk factors both for the development 68 and for the progression of osteoarthritis, 8 probably associated with the increase of load and stress in the joints and/or systemic changes. 25,65,66 An increase in mechanical forces caused by overweight and obesity across weight-bearing joints is probably the primary factor contributing to accelerate the degenerative process. 58 Therefore this association is thought to be different according to the joint site involved. 60,67

Another possible way to explain the effect of body mass index (BMI) on osteoarthritis is the pro-inflammatory action of fat 49,50; a systemic low-grade inflammation and through this mechanism associated with osteoarthritis. 49,50 Inflammation can be present as a local process but it can also have a systemic role. 25,48 Emerging data showing a crucial role for adipocytes in the regulation of cells present in bone, cartilage, and other tissues of the joint could also may be implicated in the pathophysiology. 68 Other anthropometric measures, such as body composition, fat distribution and height, were also studied and, in general, a positive association was also found. 60,70 Although they are less studied than weight and BMI, the independent effect of these variables is very difficult to measure since they are strongly related with weight. 71

Excessive joint activity/stress is potentially aetiologically linked to osteoarthritis. 72 Occupations involving repetitive, load-bearing activities are also associated with the development of the disease. 48 Manual/physical work was found to be a risk factor for knee, 72,73 hip 67 and hand osteoarthritis. 74 Low socio-economic status measured by a low educational level is related with blue collar activities and thus with a higher prevalence of osteoarthritis. 39,48,69

Physical activity confers a range of health benefits including joint health, muscle strength and weight management. 75 Moderate/leisure physical activity levels appear to protect from osteoarthritis; 76 on the other hand, high physical activity levels seem to increase the risk. 77 This is probably due to the higher risk of injuries associated with sports activities. For example, a history of regular sports participation was found to be a risk factor for knee osteoarthritis 66 and a history of high-impact physical activity has been linked to the development of hand osteoarthritis. 74

Nutritional factors may also have an important role in osteoarthritis. Antioxidants are thought to confer protection against the disease progression and like in other age-related diseases 49 Chondrocytes are potent sources of reactive oxygen species, which may damage cartilage collagen and synovial fluid hyaluronate, the macromolecule that accounts for the viscosity of synovial fluid. 78 Since micronutrient antioxidants provide defence against tissue injury, high dietary intake of these micronutrients could be postulated to protect against osteoarthritis. Results indicate that a high intake of vitamin C may be associated with a lower risk of knee osteoarthritis progression, but does not appear to prevent the onset of disease. 79 There is also evidence from longitudinal studies that low dietary and serum levels of vitamin D may be associated with the development of hip osteoarthritis. 76

High bone mineral density 25 is also thought to be related with osteoarthritis. 80,81 However, this is not always clear and associations change in different populations, joint sites and can be mediated by other factors such as vitamin D status. 52 For example, Zhang et al 83 found higher bone mineral
Osteoarthritis is a metabolically active, dynamic process that involves all joint tissues. Radiography is used to assess these morphological changes; classical features are focal joint space narrowing, osteophytes, subchondral bone sclerosis and subchondral ‘cysts'. Case definition using radiology is useful because it represents an objective measure for osteoarthritis. The most frequently used radiographic definition is the 0-4 Kellgren–Lawrence (KL) score that considers a person with grade ≥ 2 as having radiographic disease. There are other currently used definitions such as Croft or Altman scores and others based on specific radiographic evaluation scores and parameters like joint space width (JSW), definite osteophytes, joint space narrowing (JSN) and bone sclerosis. All these criteria are recognized to have advantages and limitations and there is currently debate as to what are the best radiographic definitions of osteoarthritis.

Radiographs are insensitive to early disease onset (initial cartilage degradation) and are in part insensitive to the disease progression, because of their poor reproducibility. Radiographs also do not visualize many important joint structures whose pathology may be central to the study of the disease (cartilage, menisci, labrum or ligaments directly). Furthermore, they provide little evidence of the existence of synovitis and imaging of effusions. Although bone is imaged, bone marrow lesions are not imaged on radiograph.

One alternative to radiographic evaluation is magnetic resonance imaging that directly visualizes most of the important anatomic structures, including hard and soft tissue structures; it can detect focal and diffuse cartilage changes and is less vulnerable to changes in joint position than radiography. Magnetic resonance imaging also can visualize damage in other soft-tissue structures in and around the joint, meniscal disruption, subchondral marrow lesions and synovitis changes. Further imaging modalities (e.g. computer tomography, sonography, scintigraphy) are seldom indicated for diagnosis and are normally used in specific situations (Table 2).

Laboratory tests on blood, urine or synovial fluid are not frequently required for the diagnosis but may be used to confirm or exclude coexistent inflammatory disease (e.g. pyrophosphate crystal deposition, gout, rheumatoid arthritis) in patients with suggestive symptoms or signs. There is a need for reliable new biomarkers and diagnostic tests that can facilitate earlier diagnosis of osteoarthritis and understand its progression.

Treatment Approaches

The understanding of osteoarthritis and its manifestations has expanded in recent years; so have the therapeutic and

### Table 2 - Differences between radiographic and magnetic resonance imaging in osteoarthritis evaluation

<table>
<thead>
<tr>
<th>Radiographs</th>
<th>Magnetic Resonance Imaging</th>
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</thead>
<tbody>
<tr>
<td>Low-cost exam</td>
<td>High-cost exam</td>
</tr>
<tr>
<td>Short time to execute and evaluate</td>
<td>Prolonged time to execute and evaluate</td>
</tr>
<tr>
<td>Most commonly used imaging technique</td>
<td>Not so frequently used, however the most precise imaging technique. Allows to confirm/exclude other diseases</td>
</tr>
<tr>
<td>Allows to evaluate joint space width and joint space narrowing</td>
<td>Images the joint as a whole organ</td>
</tr>
<tr>
<td>Only bone imaging</td>
<td>Bone, cartilage, menisci, labrum, ligaments and all soft tissues imaging</td>
</tr>
<tr>
<td>One-dimensionally evaluation</td>
<td>Three-dimensionally evaluation</td>
</tr>
<tr>
<td>Confirm disease diagnosis and some aspect of its progression</td>
<td>Understanding early disease onset and the natural history of the disease</td>
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treatment options to manage the disease. The major goals of treatment are pain control with minimal adverse effects, maintenance or improvement of joint mobility and function, and improved health related quality of life. Treatment should be tailored to each individual. Because no single therapy is adequate, the major clinical guidelines for disease management generally agree that therapy should involve a combination of non-pharmacologic and pharmacologic therapies.

The American College of Rheumatology and European League Against Rheumatic Diseases recommendations were recently reviewed. Pharmacologic modalities recommended for the initial management of patients with osteoarthritis include acetaminophen (paracetamol), oral and topical non-steroidal anti-inflammatory drugs, tramadol, and intra-articular corticosteroid injections, glucosamine, chondroitin sulphate and other nutritional supplements. Intra-articular hyaluronic injections, duloxetine, and opioids are conditionally recommended in patients with an inadequate response to initial therapy. Surgical procedures are advised in patients with a long course of disease and/or untreatable pain or disability with non-surgical methods: surgical options include lavage/debridement, correction osteotomy and arthroplasty. Non-pharmacologic modalities for osteoarthritis are quite diverse but broadly divided into educational and physical approaches. Educational approaches are based on lifestyle patterns changes (including diet and exercise) and joint protection techniques and walking aids. Physical exercises include aerobic activity, muscle strengthening and range-of-motion exercises. Physiotherapy strategies such as electrotherapy, thermal modalities and manual therapy are also recommended according to each patient.

Although current therapeutic approaches are primarily symptomatic in nature, there is nevertheless the potential to use available treatments to ameliorate the effects of osteoarthritis on quality of life and to potentially reduce the costs associated with the disease. The application of these new sources of knowledge about the disease process holds promise for the development of new, potentially disease-modifying pharmaceuticals.

CONCLUSION
Osteoarthritis poses a substantial and increasing burden on individuals and society. Advances in the understanding of osteoarthritis have revealed new aspects of the pathogenesis and progression of the disease. There seems to be growing recognition that osteoarthritis can have a multifactorial etiology that results from the interaction of several modifiable and non-modifiable risk factors. The correct understanding of all aspects involving this condition can help to improve the identification of osteoarthritis patients allowing early treatment strategies and also that correct public health measures can be taken.

CONFLICTS OF INTEREST
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REFERENCES