The burden of osteoarthritis: the societal and the patient perspective

Osteoarthritis (OA) is a highly prevalent disease affecting mainly knees, hips and hands. It has potentially devastating effects on health-related quality of life and will represent an increasing economic burden in the future. Moreover, pain and physical disability brought about by OA also affect social functioning and mental health, further diminishing the patient's quality of life. The burden of OA is therefore considerable, both from a societal and individual patient perspective. OA is a multifactorial disease with age being the major risk factor. As a consequence of aging populations in western and developing countries, OA will contribute to an increase of health-related burden for individuals as well as for the society. Both pharmacological and nonpharmacological treatment modalities are important, but the choice of therapy in individual patients must take into account evidence for effectiveness and individual factors.

KEYWORDS: burden ■ costs ■ imaging ■ impact ■ individual ■ measures ■ osteoarthritis ■ outcome ■ society ■ therapy

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Osteoarthritis (OA) is the most common joint disorder in the world, and occurs frequently in elderly individuals, with pain being the most prominent symptom in most people with arthritis [1–4]. Therefore, OA causes impaired quality of life [5]. Musculoskeletal diseases, including OA, are very common and were a driving force for the initiation of the 'Bone and Joint Decade' [6]. OA is a chronic joint condition, characterized by loss of articular cartilage and new bone formation. It has been considered a disease of the joint, but, recently, more attention has been focussed on the involvement of the joint environment [7].

The burden of OA on society can be described by addressing occurrence and economic consequences. Methods for measuring the impact of the disease on the individual include clinical manifestations, outcome measures and demonstration of OA by imaging modalities. The objective of this article is to describe the burden of OA on society and the individual.

Societal perspective

General aspects

Osteoarthritis is perceived as a growing problem. In the USA, the number of individuals with OA has increased by approximately 6 million affected individuals, to 26.9 million during the period of 1995–2005 [4]. This increase probably reflects the aging population, but other factors, such as increasing obesity or more sensitive methods for detection of OA, may contribute to the higher numbers.

Musculoskeletal conditions are the most common cause of severe long-term pain and physical disability [8]. Knee OA is a major cause of impaired mobility, particularly among women. In 1990, OA was already estimated to be the eighth-leading nonfatal burden of disease in the world, accounting for 2.8% of total years of living with disability, similar to the burden of schizophrenia and congenital anomalies [9]. In 2000, OA was considered to be the sixth-leading cause of years of living with disability at a global level, accounting for 3% of the total global years of living with a disability [201]. In high-income countries it has been projected that OA will be ninth on a list of causes of disability-adjusted life years by 2030 [10].

Comparative data for the impact on quality of life measures of rheumatic diseases and other chronic conditions in population-based studies are practically nonexistent in most countries [11]. When reflecting on the burden of OA in the population, one approach could be to focus on knee pain. Above the age of approximately 55 years, knee OA outweighs other causes of pain (e.g., cartilage injuries and ligament damage) [12], and radiographic knee OA is the most common cause of knee pain [13,14]. Pain in knee OA is mainly consistent but may also be present as an inconsistent complaint in many patients [15].

Economical aspects

The high prevalence of OA and the impact on the individual indicate that resources need to be increased to improve the quality of life of

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individuals in the future. Resources will apply for joint surgery, rehabilitation, pharmaceutical treatment and homecare. Healthcare providers will meet demands of an aging population that still expects to experience a high quality of life. Whether healthcare providers, or healthcare systems on a higher level, will succeed to meet these expectations, depends on several factors such as therapeutic advances, realistic expectations and allocation of resources.

Although OA has a high prevalence, economic analyses of its burden are often not calculated specifically for OA but are lumped together with other musculoskeletal conditions, without identification of the contribution of OA. OA leads to a significantly higher probability of absenteeism and more days missed from work, and a recent analysis from the USA estimated the annual per capita absenteeism costs were US$469 for female workers and US$520 for male workers [16]. In an economic analysis from the 1990s, performed in five industrialized countries (Australia, Canada, France, the UK and USA), the economical costs of musculoskeletal disorders amounted to between 1 and 2.5% of the gross national product of the countries involved [17].

In a 'cost of illness' study of the economical burden of OA, the total annual cost of the condition was estimated to be US$4900 per OA patient, using a Canadian cost template from 2000 [18]. In another study, the average annual direct medical, drug and indirect work-loss costs per OA patient were US$8601, 2941 and 4603, respectively [19]. A Spanish study calculated indirect and direct costs of €1500 annually for patients with hip or knee OA [20].

The burden of OA on society can also be described using absolute disability-adjusted life years, and this burden is growing in both developed and developing countries [21].

Obviously, disease-related factors contribute to costs and, in a Canadian study, total costs attributable to OA in the hip and knee were three-times higher in patients with high versus low disability (Western Ontario and McMaster Universities OA Index [WOMAC] score ≥55 vs <15) [22]. Thus, although the total individual disease burden of OA is lower than in rheumatoid arthritis, total direct and indirect costs of OA are higher because the prevalence of OA surpasses rheumatoid arthritis.

Classification of OA

A stratification of OA with respect to disease patterns and subsets has been suggested, considering mechanism of onset (primary or secondary OA), stage of disease progression, distribution of involved joints (e.g., generalized vs localized OA), inflammatory levels and effusion [23]. Definition of subsets in OA may help to understand the disease and disease characteristics, but the utility of stratifying OA will depend on whether it provides clinically useful information. Furthermore, it will be necessary to derive adequate stratification that can serve in clinical trials where specific interventions are examined for subsets of patients.

When defining OA for epidemiological studies the inclusion of radiographic findings is preferred [24]. The course of the disease varies but is usually progressive, as demonstrated by increasing radiographic abnormalities over time. Symptoms can be relieved and function improved, especially in relation to joint replacements.

A diagnosis of 'self-reported doctor-diagnosed arthritis' is today thought to provide the most credible estimate for overall arthritis prevalence [25]. Age remains the strongest single risk factor for OA development. However, among the elderly reporting knee pain over the age of 65 years, only approximately half had radiographic evidence of OA [26]. Yet another study adds evidence to the observation that pain and OA, as determined by radiographic changes, do not correlate well with each other [27]. As a consequence of poor correlation between symptoms and radiographic evidence a preferred definition of OA includes both symptoms and demonstrated radiographic damage. As such, the definition by the American College of Rheumatology for OA is predominantly used for knee and hip OA [28,29], while radiographic changes are not a requirement for hand OA [30]. These published criteria standardize and define OA by location.

Incidence & prevalence

Cumulative lifetime prevalence for symptomatic knee OA is 10.2 and 6.2% for hand OA [11]. In surveys from Canada, the USA and western Europe, the prevalence of physical disabilities caused by a musculoskeletal condition has repeatedly been estimated to be 4–5% of the adult population, of which rheumatic disease accounted for approximately half [31]. There are significant numerical gaps in population studies from eastern Europe, South America and Africa. It is therefore difficult to estimate the future burden of OA and currently only uncertain estimates can be used [201]. Global estimates are that 9.6% of men and 18.0% of women aged 60 years

or more have symptomatic OA [9]. A prevalence of 18% for OA has recently been reported from Greece in response to a questionnaire mailed to the population [32].

Knee OA

The knee is the most frequently affected joint in OA. In the Framingham Study, the presence of OA was defined when there were knee symptoms together with radiographic changes (grade two according to the Kellgren and Lawrence [KL] classification [24] on the same side). The prevalence of radiographic OA increased from 33% in the 60–70 years age group to 44% in those over 80 years of age. Overall, symptomatic knee OA was present in 9.5% of the population and increased with age, especially in females [33].

In the Johnston County Osteoarthritis Project, knee OA was assessed in over 3000 participants, and knee OA was diagnosed if a KL score of two or higher was present when at least one knee gave symptoms [34]. The prevalence of knee OA increased from 26% in the age group of 55–64 years to almost 50% among those 75 years and older.

In the National Health and Nutrition Examination Survey (NHANES) III, the prevalence of radiographic knee OA in individuals over the age of 60 years was 37%, and 12% for symptomatic radiographic knee OA [35], demonstrating that radiographic changes are more frequent than radiographic changes and symptoms together. A large Dutch cohort of more than 6000 participants aged over 45 years included radiographic examinations, and the prevalence, given as average of both knees with a KL grade of at least two, increased in both genders with age, but mostly in females [36]. A Greek study found lower estimates [37], while a Japanese study found higher numbers [38]. In China, the estimated prevalence of symptomatic and asymptomatic knee OA in the community was 7.2 and 37.4%, respectively [39]. In a Norwegian population survey, knee OA was slightly more prevalent than hip and hand OA [40].

Incidence figures for symptomatic knee OA of over 1% per annum for females and 0.8% for males were calculated based on the database of a health maintenance organization in the USA [41], comparable with data from the Framingham Study [42]. In the Chingford Study, the incidence of radiographic knee osteophytes in females was 3.3% per year [43]. In Bristol, UK, the rates of incidence and progression for knee OA were 2.5 and 3.6% per year, respectively [44].

Hip

An age-related increase in OA in the hip joint has been observed from 0.7% in the 45–54 years age group to 17% in the over 75 years age group [45]. In the NHANES study, the prevalence of hip OA among females aged 65 years or more varied between 2.1 and 7.6%, dependent on the definition that was used [46]. Hip OA is less common than knee OA, and a Swedish survey found a radiographic prevalence of 1.9% among men and 2.3% among women older than 45 years [47].

Hands

In a Dutch study, more than half of all individuals (males aged 65 years or more or females aged 55 years or more) had radiographic OA involvement of distal interphalangeal joints [36]. The yearly incidence in the database from a health maintenance organization was 0.35 and 0.21% for males and females, respectively [41].

It has been concluded that few reliable data on the incidence of OA are available due to problems defining OA and determining the onset of the disease. There are also differences through localizations [201]. Given that OA constitutes an irreversible disease, its prevalence increases indefinitely with age. In younger age groups, for example those aged 45 years or less, men are affected more often than women, whereas females are affected more frequently among those aged 55 years or more [48].

There are no clear indications that OA should be more prevalent in some geographic areas of the world than in others. However, African–American women are more likely than white women to develop OA of the knee [49,50]. An age-related decrease in cartilage in the knee has recently been shown among females in the normal population [51].

Risk factors of OA

To assess the burden of OA on society and to manage the disease in the best possible way in the individual, it is important to increase our knowledge regarding the predictors of progression of OA. Risk factors for OA may be either non-modifiable or modifiable.

As shown by epidemiological data, age is the strongest predictor of the development and progression of radiographic OA. The risk of incident OA can be calculated, combining the contribution of several factors, for example age, gender, BMI and biomarkers [52]. Genetic susceptibility to OA has been documented and molecules involved in the signaling cascades of articular pathology have been identified. Different

pathways that are involved in the pathological process are also candidate intervention targets for pharmacological therapy. Candidate gene studies and genome-wide linkage studies have identified susceptibility genes for large-joint OA in the bone morphogenetic pathway (e.g., *GDF5*), the thyroid regulation pathway (*DIO2*) and apoptotic pathways. Genome-wide association studies have also identified structural genes (*COL6A4*), inflammation-related genes (*PTGS2*/*PLA2G4A*) as well as *GPR22* and four other genes associated with OA [53]. For example, the risk for end-stage hip and knee OA is related to the promoter polymorphism rs20417 of the *COX-2* gene [54]. While genetic factors may account for the development of OA in many individuals, a significant component of environmental factors remains important.

Malalignment in the knee joint is known to change the load distribution in the femorotibial joint, with greater load on medial femorotibial compartment in varus knees and greater loads through the lateral compartment in valgus knees. Malalignment has also been identified as an important risk factor for structural changes of the cartilage diagnosed by MRI [55]. Varus alignment, in particular, compared with normal alignment, was found to be associated not only with progression of knee OA, but also with development of knee OA [56].

Obesity (high BMI) is an acknowledged risk factor for the development and progression of OA in the knee. Prospective data from the Framingham population have shown that obesity is a risk factor for onset of knee OA [57,58] and that radiographic OA is a consequence of obesity. Obesity serves as an example to show how comorbidity becomes a risk factor of OA itself. Other studies have demonstrated obesity to be a risk factor for the development of OA of the knee [57–59] and the hand [60]. An increase in BMI over 10 years was found to be associated with bone marrow lesions, which are known to precede cartilage loss [61]. In a cross-sectional observation, a high BMI was associated with knee and hand OA, but not with hip OA in a Norwegian study [62].

Another major modifiable risk factor for the development of knee OA is constituted by meniscal tear damage with a sevenfold increase of subsequent OA in symptomatic individual suffering meniscal damage [63]. Trauma and certain physically demanding activities or occupations are also risk factors for the development of OA of the knee and hip [64]. Anterior cruciate ligament injury is a physical risk factor for the development of knee OA, which is mostly seen in young adults as a consequence of sports injuries [65]. Long-term farming was, in one study, associated with the greatest relative risk for OA [66].

In another a study, the evidence for risk factors of OA progression was reviewed, examining a wide array of variables [67]. Strongest evidence for the prediction of OA progression was found to be malalignment in the knee and atrophic bone response in the hip, while some evidence was seen for age, other biomechanical abnormalities and concentration of hyaluronic acid [67]. **Figure 1** schematically demonstrates risk factors that may contribute to OA.

Cost–effectiveness of therapy

Total joint replacement is a frequently applied procedure in OA of the hip and knee joint, and the importance of these surgical interventions reflects the burden of disease not only for the patient, but also on a societal level. In the USA, during the year 2000, almost 125,000 unilateral primary total knee replacements were performed among Medicare beneficiaries [68], demonstrating that total knee replacement is one of the most frequently performed orthopedic procedures, at least in the USA. Increasing obesity in the population was one factor that led to more procedures with total hip and knee replacements. This is in contrast to recent developments in surgical replacement therapy in rheumatoid arthritis where a decrease has been observed in the USA [69] and in Europe [70]. During the 1990s, joint replacements for knee and hip joints in hospitals of the British NHS have shown a marked increase, which follows trends in the epidemiology of OA and hip fractures [71]. As techniques for applied surgery improve, surgery becomes feasible in increasingly older patients, and revisions have also increased, especially in the 60-years-and-over age group. If trends continue, approximately 50,000 primary hip and knee operations each are forcasted for 2010 [71].

The cost–effectiveness of hip and knee replacements is considerable, but hip replacement is also among the most cost-effective interventions in medicine, amounting to less than US$10,000 per quality-adjusted life year [72]. The Short Form-36 (SF-36) is a generic questionnaire that can be used to document the severity of OA and the benefits of total joint arthroplasty. Data from the SF-36 substantiate total joint replacement as one of the most successful modern surgical procedures and support arguments for making total joint replacement procedures available [73]. Still, although total joint replacement is one

of the most cost-effective operations available, in many countries patients cannot be treated with surgery due to inability to pay or due to inadequate resources [74].

Patient perspective

Clinical manifestations of OA

In addition to the loss of articular cartilage during the development of OA, structural and functional alterations are seen in all compartments of the joint including ligaments, tendons, capsule, synovial lining and periarticular bone [75]. The focal areas of loss of articular cartilage are associated with hypertrophy of bone (i.e., osteophytes and subchondral bone sclerosis). Clinical findings are pain, tenderness, limitation of movement, occasional effusion and variable degree of local inflammation. OA can occur in any joint, but is usually divided into three subtypes based on involvement in knee, hip and hand. Sometimes the term 'generalized OA' is used in patients with simultaneous OA manifestations in several locations. Synovitis can be observed early in OA [76]. Synovial inflammation and the release of mediators, such as cytokines, eicosanoids and growth factors by the inflamed tissue, are considered as important, both for the development and the progression of OA [77].

While any joint can be affected in OA, specific joint involvement of the hip, knee or hand are dominating the clinical picture of patients with OA. In the hip, symptoms are usually insidious at onset. Pain in the groin and rescued motion, especially in internal rotation, are typical, as is pain around the trochanter, in the buttocks, sciatic region or projected to the knee. In the hands, erosive OA is a variant with prominent distal interphalangeal or proximal interphalangeal involvement. Affection of the carpometacarpal joint in the thumb may compromise function in the whole hand. Flares of inflammation may drive deformation and joint erosion.

Outcome measures

Clinical measures are needed for assessment of disease impact, for monitoring of the disease process and for evaluation of the outcome of treatment. We still lack knowledge as to which outcomes are important from a patient perspective. If patients have different views on the burden of disease, dependent on whether their hip, knee or hands are affected, then stratification of the disease is important, and outcomes, for example for hand OA, should be specific. To date, recommendations regarding which outcomes should be measured come from expert consensus, and criteria for improvement have, for OA in general, been defined from clinical databases [78].

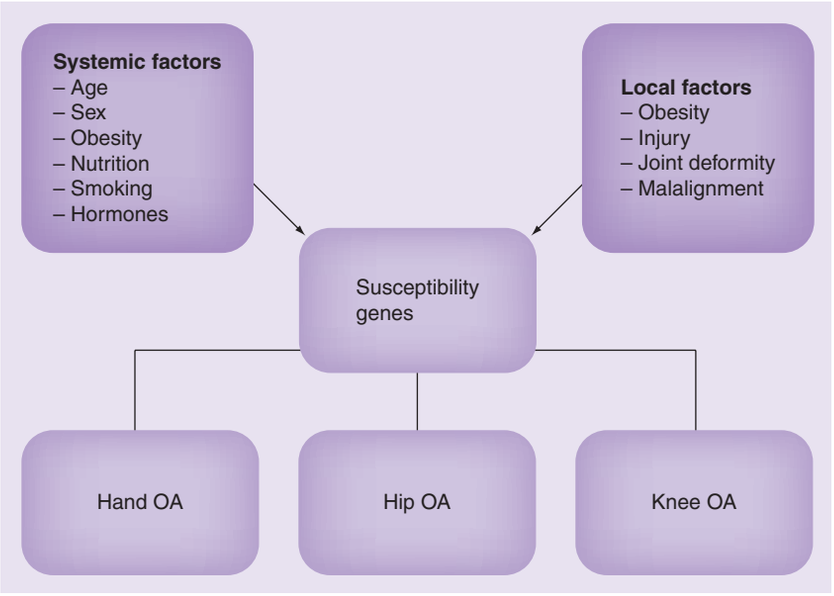

Figure 1. Systemic and local factors carrying risk for osteoarthritis in the knee, hip or hand.
OA: Osteoarthritis.

Appropriate validated and frequently used outcome measures can be generic or condition-specific, multidimensional or unidimensional. Generally, for OA, the recommendations for assessments include pain, physical function and patient global assessment [79,80]. Health-related quality of life is an umbrella term and sums up the impact of a disease on various dimensions of health in the patient's life. Pain and physical function are essential constituents of health-related quality of life, but additional areas include stiffness, mental health, sleep disturbance, fatigue, social interaction, vitality and several other domains. Health-related quality of life can be assessed by several established patient-reported outcomes [81].

The SF-36 is the most widely used generic, multidimensional outcome measure [82]. A multidimensional arthritis-specific instrument is the Arthritis Impact Measurement Scales (AIMS)-2 [83]. The Health Assessment Questionnaire (HAQ) [84] and the modified HAQ (MHAQ) [85] measure physical function and were developed for use in rheumatoid arthritis but are also applied in other arthritides.

For the rating of OA of the lower limbs, several multidimensional, specific questionnaires, such as the WOMAC [86], the Hip Disability and Osteoarthritis Outcome Score (HOOS) [87], the Knee Osteoarthritis Outcome Score (KOOS) [88], the index of severity for OA

of the hip (ISH) and knee (ISK) [89], and the Osteoarthritis Knee and Hip Quality of Life Questionnaire (OAKHQOL) [90] are available.

For hand OA specifically, measurements of performance, mobility, stiffness, inflammation, deformity and esthetic damage are also recommended [91]. Performance can be assessed, for example, by measurement of fine hand functioning [92] or grip strength [93]. The Moberg pickup test is a brief, simple clinical test [92].

For assessment of hand OA with questionnaires, both hand OA specific and instruments for various arthritides can be used [94]. Hand OA-specific instruments include the Australian Canadian Hand OA index (AUSCAN) [95] and the Score for Assessment of Chronic Rheumatic Affections of the Hands (SACRAH) [96]. The Michigan Hand Outcomes Questionnaire (MHQ) is a generic, multidimensional outcome measure for the hands [97]. Specific patient-reported outcomes for functional assessment of the hands are the Functional Index for Hand Osteoarthritis (FIHOA) [98,99] and the Cochin index [100,101]. The Self-Efficacy Scales assess coping abilities in rheumatoid arthritis patients [102], can also be used in OA. A questionnaire addressing the patient's perspective has also been developed [103].

Two hand OA-specific instruments, the AUSCAN and FIHOA, have recently been compared and are both valid and reliable in clinical practice [104]. Stiffness can be measured as length of morning stiffness or the stiffness subscales of the AUSCAN [95] and the SACRAH [96], although it is not currently clear how relevant stiffness is to patients with hand OA.

For easy application in clinical practice, the advantage of instruments such as WOMAC or AUSCAN, and the HAQ is that they are self-administered instruments with intuitive interpretation of results, while the SF-36, by contrast, requires a more complicated scoring and is rarely used in clinical settings [105]. In knee OA, although both the WOMAC and SF-36 can be used to assess various domains of quality of life, WOMAC may be more responsive than the SF-36 instrument to detect changes in function [106]. Table 1 presents outcome measures that are often used for assessment of OA in lower limbs and hands.

Another outcome is constituted by inflammation that can be assessed as joint swelling, night pain and duration of morning stiffness [78]. Joint deformities of the hands include presence or absence of bone enlargement, Herberden and Bouchard nodes, and axial deviation of first carpometacarpal joint in the thumb. Esthetic damage as a consequence of the disease is known to be important to patients and can be assessed by the MHQ [78].

The burden of disease in individual patients can also be assessed according to the International Classification of Functioning, Disability and Health (ICF) [107], and core sets have been developed to use the ICF for OA in clinical practice [108]. This classification involved domains of body functions, structure, and activity and participation. However, to date, the ICF has not been sufficiently validated for use in daily practice in patients with OA. The ability to perform a specific task in their daily life may be more important to patients than their ability to perform a specified task item in a test situation or in a questionnaire [109].

Composite indices are being used to assess disease activity in other rheumatic diseases such as rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. Similar efforts are undertaken to develop an index that could be used to evaluate changes in disease activity in hand OA [110].

Impact of OA on the individual

Individuals with lower limb OA experience reduced strength of the quadriceps muscle, impaired proprioception, affected balance and increased falls [111–113]. Many of the physiological

Table 1. Outcome measures often used in osteoarthritis of lower limbs and hands.

Localization of osteoarthritis	Outcome measures	Ref.
Lower limbs	WOMAC	[86]
	KOOS	[88]
	HOOS	[87]
Hands	AUSCAN	[95]
	FIHOA	[98,99]
	SACRAH	[96]

AUSCAN: Australian Canadian Hand Osteoarthritis Index; FIHOA: Functional Index for Hand Osteoarthritis; HOOS: Hip Disability and Osteoarthritis Outcome Score; KOOS: Knee Osteoarthritis Outcome Score; SACRAH: Score for Assessment of Chronic Rheumatic Affections of the Hands; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

characteristics of OA are closely related to muscle strength and thus muscle strengthening seems to be an obvious objective in the treatment of OA, particularly knee OA.

While we have information on risk factors in OA, little is known regarding the course of disability over time in patients suffering from OA. In a systematic review on the impact of nontraumatic hip and knee disorders on health-related quality of life, clear differences between subjects and the reference population were found, especially for physical, but also for mental and social measures using SF-36 [114].

The clinical burden of OA is considerable. A French survey, conducted nationwide among a sample of more than 5000 physicians, compared functional limitation rates for patients with OA with age- and sex-matched controls obtained from an earlier population-based national survey on disability [115]. In this sample, more than 81.5% of patients reported limitations in their activities of daily living, including basic tasks, leisure activities and work. Employment changes occur in the lives of many individuals with OA and there is a complicated relationship between work productivity loss (absenteeism), and a number of individual and other factors in OA [116], as also seen in rheumatoid arthritis [117]. Mobility limitations outside the home were reported by 61.1% of OA patients, compared with 10.2% of control subjects. Similarly, significantly greater percentages of patients with OA had limitations in terms of mobility inside the home and activities of daily living (e.g., grocery shopping, house cleaning, dressing, personal care and meal preparation). Among subjects who were employed, 64.4% of OA patients reported significant limitations, compared with 14.3% of those without OA [115].

Rheumatoid arthritis is generally perceived as a severe and disabling disease, but recent data suggest that hand OA and rheumatoid arthritis have a similar impact on health-related quality of life [2,118]. In a Norwegian study, 190 female hand OA patients were compared with 194 female patients with rheumatoid arthritis of the same age. Health-related quality of life was measured with the AIMS2, SF-36 and its preference-based single utility index SF-6D, HAQ, Self-Efficacy Scales, and visual analog scales for pain and fatigue [2]. In the study, hand OA patients had higher levels of physical functioning than patients with rheumatoid arthritis, while pain levels were higher in OA patients, indicating that the overall impact of the disease on health-related quality of life was similar [2].

Waiting for joint replacement can contribute to reduced health-related quality of life for patients with OA, and being on a waiting list for joint replacement also contributes to high psychological distress [119]. During the period of time that a patient spends being on a waiting list, the disease-specific scores deteriorate and inflict avoidable disease burden [120].

Patients with OA in the metacarpal joint report more pain than when OA is localized in the interphalangeal joints [121]. Patients with erosive OA experience more pain, more functional limitation, less satisfactory hand function and worse hand mobility compared with patients without erosions [122].

Comorbidities

As the prevalence of OA steadily increases with age, diseases such as hypertension, diabetes and obesity are common comorbidities in patients with OA. Evidence suggests that patients with OA are at higher risk than the general population for several comorbid conditions, including cardiovascular disease [123]. These comorbidities add considerably to the costs and complexity of treatment of patients with OA.

Using data from the NHANES III in the USA, Singh and colleagues estimated the prevalence of traditional risk factors for cardiovascular disease among US adults with OA [124]. Approximately 40% of people with OA have stage I–III hypertension, as defined by the sixth Joint National Committee guidelines, compared with approximately 25% of the general population without OA. The percentage of patients with OA with comorbid hypertension is likely to be higher if the newer, more stringent seventh Joint National Committee categorization for hypertension is used [125]. Similarly, the percentage of people with OA who have concomitant diabetes mellitus (11%) is significantly higher than in the general population (6%) [124]. Other cardiovascular manifestations are similarly more prevalent among OA patients than among the general population, including hypercholesterolemia (32 vs 24%), low high-density lipoprotein cholesterol (13 vs 12%) and renal impairment (37 vs 27%) [124]. Hand OA in older women is also related to atherosclerosis [126]. These findings may have therapeutic consequences since the use of nonsteroidal anti-inflammatory drugs is associated with increased blood pressure and risk for thrombotic cardiovascular events, and many patients in need of nonsteroidal anti-inflammatory drugs have a high prevalence of gastrointestinal or cardiovascular risk factors [127].

Psychosocial factors also contribute to the burden of disease in OA. A recent review has shown that psychological distress and fatigue are factors occurring at a significantly higher rate in individuals with OA than individuals without OA [128].

Imaging modalities

The scoring system by Kellgren and Lawrence has been used for decades for the demonstration of radiographic damage as well as for the grading of radiographic abnormalities [24]. This system assesses the severity of radiographic damage by considering osteophytes and joint-space narrowing as well as sclerosis and subchondral cysts. In recent years, other scoring systems have been developed and MRI [129], as well as ultrasound [130–132], are new imaging modalities employed in OA. Application of MRI in recent studies allowed the examination of relationships between bone marrow lesions, cartilage volume and symptoms [133–135], or the effect of biodynamic effects on bone marrow lesions [136]. Bone marrow lesions in pain-free people are reversible, but are related to BMI [137].

Hand OA patients have a higher bone mineral density, as measured by dual-energy x-ray absorptiometry, than population-based controls. The lack of correlation between bone mineral density and disease duration or severity does not support the hypothesis that higher bone mineral density is a consequence of the disease itself [138].

Monitoring structural damage in OA is considered a primary outcome when the use of structure-modifying therapies is to be examined [139]. Traditionally, the assessment of radiographs in OA has used the KL scoring system has been used [24], but now other scoring systems have also been suggested. The atlas by Altman *et al.* [140] has been revised and is, as such, used as the Osteoarthritis Research Society International (OARSI) scoring atlas [141]. Other scoring methods for OA of the hand have been developed [142,143] and new imaging modalities are emerging, including ultrasound [144] and MRI [110]. There is a need to compare different scoring systems, and such tasks include combined work, for example the Outcome measures for Rheumatic Diseases (OMERACT)-OARSI imaging workshop [145,146]. New methodologies are thus developed applying the OMERACT filter: truth, feasibility and discrimination. These new modalities need good discriminative abilities in order to be applied when new drugs are tested for structure-modifying effects in OA. Relevant radiographic progression in hip and knee OA has also been defined with cut-offs, facilitating interpretation of study results [147].

Implications for therapy

As a result of these trends of increasing disease burden of OA, the question of how best to treat OA is becoming increasingly urgent. As we now better understand the pathophysiological processes of OA, promising therapeutic targets have been identified.

To predict efficacy of treatment and prognosis of OA, there is a need to further develop outcome measures, treatment modalities and use of biomarkers [148,149]. Several new classes of molecules that inhibit one or more OA pathophysiological processes have been discovered, and a number of these compounds are under clinical evaluation to test their potential to modify and thus improve the disease process of OA with disease-modifying OA drugs. Possible and promising mechanisms are suppression of synovial inflammation, inhibition of cartilage degradation, inhibition of subchondral bone modeling and cartilage repair [150].

Current treatment goals include reducing pain, maintaining or improving joint mobility, limiting functional impairment and improving health-related quality of life. Future goals include prevention of structural progression. These recommendations support that both pharmacologic and nonpharmacologic treatment are important parts of the total management program. Self-care, exemplified by the self-care management program, aims at increasing the ability of individuals to cope with the consequences of the disease [102].

The NICE guidelines recommend that treatment of OA should be driven by the effect of OA on the individual's function, quality of life, occupation, mood, relationships and leisure activities [151]. Treatment plans should be developed in coordination with the individual suffering from the disease, taking into account comorbidities that compound the effect of OA and ensuring that the patient has an understanding of the risks and benefits of treatment options.

The NICE guidelines categorize treatment into three groups: core treatments, adjunct nonpharmacologic treatments and adjunct pharmacologic treatments. Core treatments include access to information and education, strengthening exercises and aerobic fitness training, and weight loss in cases of obesity. Topical nonsteroidal anti-inflammatory drugs

and paracetamol are considered first-line pharmacologic treatments for OA. Evidence-based, expert consensus recommendations for the management of OA have also been published by OARSI [152] and have been updated for new evidence [153]. These recommendations represent a synthesis of 23 treatment guidelines for the management of hip and knee OA. Over the past few years, a lot of interest has been given to the possible effects of glucosamine and chondroitin supplementation in OA. An update has reported currently diminished effect sizes for glucosamine and chondroitin [153].

While structural modification is often out of reach in clinical practice, the European League Against Rheumatism recommends a combination of pharmacological and nonpharmacological care for relieving the burden of knee, hip and hand OA [5,154,155]. The clinical indication for total joint replacement is dependent on individual judgment. There is little consensus among orthopedic surgeons and it is considered difficult to determine which level of functional limitations merits surgery [156]. As longevity of the prosthesis has increased and perioperative outcomes have improved, a decision to have surgery has been suggested to be driven by patients' preferences, appreciating that the likelihood of functional benefit is higher when the preoperative functional status is better [156]. With respect to perioperative outcome of prosthesis surgery, age is a predictor of death and medical complications [157], and it is well known that hospital size and the number of surgeries performed have an impact on mortality. While knee arthroscopy with lavage has been a common therapeutic procedure in OA, lack of evidence of an effect beyond placebo [158] has led to less frequently performed arthroscopic lavage and debridement [74].

Nonpharmacologic & nonsurgical treatment

Lifestyle change, and, as a consequence, weight reduction, is a potential treatment that can alleviate the burden of OA. The Framingham Study showed that a reduction of BMI by two units reduced the risk of symptomatic knee OA by 50% in women [159]. In knee OA, greater improvements in pain and disability were found in the group who underwent both weight control (dietary control and aerobic exercise) and acupuncture in addition to electrotherapy than in the groups who underwent either weight control or electrotherapy alone [160]. The mechanism by which excess weight causes OA is still poorly understood. Nevertheless, controlling obesity is important not only for OA, but for musculoskeletal health [161], and exercise and weight loss, as well as self-management programs, are basic elements in the treatment of OA [162]. Reducing body burden (i.e., bodyweight) will thus reduce disease burden of OA. In general, there is more evidence of the benefits of weight loss in knee OA than in hip and hand OA [162,163]; however, importantly, obesity is not only a modifiable risk factor for OA, but weight reduction may also reduce the progression of OA.

Systematic reviews have evaluated the effect of land-based exercise for hip and knee OA, demonstrating improvement in pain, function and global assessment [164,165]. The effectiveness of nonpharmacological and nonsurgical treatments has been evaluated in three overviews of systematic reviews. For hand OA, there is some evidence for the improvement of pain by topical capsaicin, as compared with placebo, based on single randomized controlled trials, and favorable functional outcomes for exercise and education compared with OA information alone are found. There is also limited evidence that splinting of the thumb carpometacarpal joint can reduce pain in hand OA [166]. In hip OA, available data from randomized controlled trials do not supply sufficient evidence to support beneficial effects of therapeutic exercise [167]. There is moderate-quality evidence that acupuncture and diacerein have no effect on pain and function in hip OA, and there is low-quality evidence that strengthening exercises and avocado/soybean unsaponifiables reduce pain, and that diacerein decreases radiographic OA progression [168]. For knee OA, there was high-quality evidence that exercise and weight reduction reduce pain and improve physical function [169]. A systematic review on the long-term effects of exercise therapy on pain and physical function in patients with OA of the hip or knee demonstrated that short-term effects were not sustained over at least 6 months [170]. Physical activity seems to have differential effects on various structures on the knee but without increasing joint space narrowing [171]. There is moderate-quality evidence for the effect of acupuncture and transcutaneous electrical nerve stimulation in relieving pain [169].

These studies underline the great difference in the amount of published high-quality randomized controlled trials and reviews in the fields of knee, hand and hip OA. The most striking finding of the umbrella reviews summarizing

overviews on hip and hand OA is the paucity of available high-quality systematic reviews. Thus, there is currently a very limited body of high-quality evidence for the effects of nonpharmacological and nonsurgical interventions for hip and hand OA. Generally, the methodological quality of the primary studies included in the systematical reviews on hip and hand OA were low to moderate, often presenting conflicting results [166,168].

Future trends

The burden of OA is expected to increase further in our societies and for the individual affected by OA. It may be difficult to give an accurate estimate for the occurrence of OA [172], but the predicted aging of the world's population, predominantly in less developed countries, will clearly increase the number of individuals affected by OA. Consequences of the disease will also remain considerable where access to arthroplasty and joint replacement is not readily available. Lifestyle factors, such as increased obesity and lack of physical activity, is a global challenge and contribute to further increase the burden of OA.

Musculoskeletal conditions cause high monetary costs to society and obtained figures emphasize how governments should invest in the future and look at ways of reducing the burden of musculoskeletal diseases, for example, with campaigns promoting exercise and prevention of obesity.

In the future, the clinical approach to OA is expected to change considerably. Patients may be classified into subsets of the disease to optimize treatments based on clinical, biochemical, and genetic measures or profiles. Furthermore, a shift from symptomatic to disease-modifying treatment is on the horizon, and clinicians need to be aware of current ongoing research and future trends in this field.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Executive summary

Context

- Osteoarthritis (OA) is a highly prevalent disease affecting mainly knees, hips and hands.
- The burden of OA describes consequences both on society and on the individual.

Societal perspective

- Today, OA is perceived as a growing problem with a population of 27 million affected in the USA alone.
- Healthcare providers will have to meet demands of an aging population that still expects to experience a high quality of life.
- The burden of OA in the society can be described using absolute disability-adjusted life years, and this burden is growing in both the developed and developing countries.
- The cost of OA is high both for total costs and for indirect work loss.
- Definition of OA subsets may help to understand the disease and disease characteristics.
- Age is the strongest predictor of OA, and other important risk factors include female gender, joint damage, malalignment, genetic susceptibility and obesity.
- Global estimates for symptomatic OA are over 10%.

Individual perspective

- Key aspects of joint symptoms in OA include pain, stiffness and reduced joint function.
- In some areas of health-related quality of life, patients with OA experience a reduction similar to rheumatoid arthritis.
- Patients with OA are at higher risk than the general population for several co-morbid conditions, including cardiovascular disease.
- Clinical measures are needed for the assessment of the disease impact, for monitoring the disease process and for outcome evaluation.
- Outcome measures in OA can be generic or disease and location specific, and include a number a questionnaires.
- OA damage has traditionally been assessed using radiographs, but now new imaging modalities such as ultrasound and MRI have been developed.

Implications for therapy

- Nonpharmacological and nonsurgical treatments currently seek to reduce pain, maintaining or improving joint mobility, limit functional impairment and improve health-related quality of life.
- Promising mechanisms to modify disease course in OA include suppression of synovial inflammation, inhibition of cartilage degradation, inhibition of subchondral bone modeling and cartilage repair.
- The clinical approach to OA is expected to change, acknowledging subsets of disease and optimizing treatment according to biochemical and genetic profiles.
- A shift from symptomatic to disease-modifying treatment is envisaged.

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