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Is osteoarthritis a gender-specific disease?

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Summary. Osteoarthritis (OA) is a multifaceted and heterogeneous syndrome. It has long been noticed that there is great variability in clinical presentation and long-term disease progression across patients with OA. The wide range of risk factors associated with OA, such as older age, hormonal status, genetic predisposition, obesity and metabolic syndrome, indicates that there may be multiple underlying pathways leading to similar outcomes of joint destruction.
The aim of this article is to conduct a narrative review on gender influence in OA patients regarding: epidemiology, risk factors, pain status and prosthetic outcomes.
Males (aged 55 and over) tended to have a significant reduction in risk for knee and hand OA compared to females of the same age. For hip OA, the risk increases at about the same rate with age in women and men but it seems to progress more rapidly in women. The lifetime risk of developing symptomatic knee OA was about 40% in men and 47% in women, whereas the lifetime risk for symptomatic hip OA is 19% for men and 29% for women.
Obesity is one of the best established risk factors for OA, especially knee OA. The prevalence of diagnosed symptomatic knee OA is much higher in obese women than non-obese women. As far as sex differences are concerned, obese women develop a higher risk of knee OA than obese men. Besides, women are more likely to complain of higher pain levels and lower function and vitality scores than men.
Finally, after total joint arthroplasty, men reported a better response in pain relief and improvement in joint function.
Although slight differences exist with regard to particular aspects of the disease, they are important to understanding the specific impact of sex on the development and progression of disease with the ultimate purpose of obtaining the proper strategy to provide better individualised treatment.

Key words: osteoarthritis, gender differences.

L'osteoartrite è una patologia di genere?

Riassunto. L'osteoartrite (OA) è una malattia complessa ed eterogenea con una grande variabilità nella presentazione clinica e nella progressione nel tempo. Lo sviluppo di OA è associato alla presenza di determinati fattori di rischio come l'età avanzata, lo stato ormonale, la predisposizione genetica, l'obesità e la sindrome metabolica.
Lo scopo di questo articolo è stato quello di condurre una breve review narrativa sulle differenze di genere in particolari aspetti dell'OA come l'epidemiologia, i fattori di rischio, la percezione al dolore e gli outcome dopo chirurgia protesica.
Riguardo all'epidemiologia, i maschi con età superiore a 55 anni tendono ad avere un rischio inferiore di sviluppare OA a carico delle ginocchia e delle mani rispetto alle donne della stessa fascia di età. Per l'OA dell'anca, non sono state rilevate differenze tra i due sessi anche se nelle donne l'OA dell'anca progredisce più rapidamente. Riguardo l'incidenza e la progressione di malattia, diversi studi affermano che il rischio di sviluppare OA delle ginocchia è circa il 40% tra gli uomini e circa il 47% tra le donne, mentre il rischio di sviluppare OA a carico delle anche si attesta a circa il 19% per gli uomini e il 29% per le donne.
Tra i fattori di rischio per OA, l'obesità è sicuramente annoverata tra i principali, in particolare per lo sviluppo di gonartrosi. Diversi studi hanno infatti dimostrato come tra le donne obese tale rischio era significativamente maggiore rispetto alle donne non obese e, riguardo alle differenze di genere, le donne obese avevano una probabilità maggiore di sviluppare gonartrosi rispetto ai maschi obesi.
Le donne, inoltre, riportano rispetto agli uomini valori più elevati alle scale di valutazioni del dolore e una peggiore qualità di vita con maggiori disabilità fisiche e funzionali.
Infine, gli uomini comparati alle donne, rispondono meglio alla terapia chirurgica di protesizzazione, riportando outcome migliori sulla sintomatologia soggettiva e sulla funzionalità articolare.
La conoscenza delle differenze di genere per determinati aspetti della malattia permette di ottenere una strategia di trattamento personalizzata per la cura dell'OA.

Parole chiave: osteoartrite, differenze di genere.

Introduction

Osteoarthritis (OA) is one of the most common conditions in the musculoskeletal disorders and is a leading cause of pain and disability worldwide. OA affects 240 million people worldwide, about 10% of men and 18% of women over 60 years of age, leading to a significant morbidities that include disability and reduced quality of life and contribute to mortality. Although OA can affect multiple joints in the body, the most common sites are the hands, knee, hip and spine[1].

Risk factors for the development of OA are well known and well-established: older age, obesity, genetic factors, diet and lifestyle. Although OA is not a cause of increased death, the hypomobility due to OA symptoms may result in excess mortality in particular when associated with comorbidities like history of diabetes, cardiovascular disease, or cancer.

The aim of this article is to provide a narrative review of the gender influence in OA. The following items were evaluated: epidemiology, risk factors, pain, mental status and outcomes in prosthetic surgery.

Epidemiology

As far as epidemiology is concerned, we can break OA down into radiological and clinical. There are multiple ways to define radiographic OA and the most common is the Kellgren-Lawrence (K/L) scale. This joint scoring system classifies OA in five levels from 0 to 4, defining OA by the presence of a definite osteophyte (grade ≥2) and more severe grades by the subsequent occurrence of joint space narrowing, sclerosis, cysts, and deformity[2].

The age-standardised prevalence of radiographic knee OA in adults age ≥ 45 was 19.2% among patients in the Framingham Study and 27.8% in the Johnston County Osteoarthritis Project. In the third National Health and Nutrition Examination Survey (NHANES III), approximately 37% of subjects age > 60 years or older had radiographic knee OA. Age-standardised prevalence of radiographic hand OA was 27.2% among the Framingham patients. Radiographic hip OA was less common: about 7% of women age ≥ 65 years in the Osteoporotic Fractures study had radiographic hip OA. However, prevalence of hip OA was much higher in Johnston County, with 27% of participants > 45 years of age showing radiographic evidence of K/L grade 2 or higher[3].

Symptomatic OA is usually defined by the presence of pain or stiffness in a joint with radiographic OA. The age-standardised prevalence of symptomatic hand and knee OA is 6.8% and 4.9%, respectively, in Framingham patients > 26 years of age. However, the prevalence of symptomatic knee OA was 16.7% among subjects > 45 of age in the Johnston County Osteoarthritis Project. About 9% of participants in the Johnston County study had symptomatic hip OA[4].

As far as sex differences are concerned, Velandai and colleagues performed a meta-analysis in OA prevalence, incidence and severity. Among patients > 55 years of age, males tended to have a significant risk reduction for knee and hand OA compared to females, but so far studies have not found a gender effect on the progression of knee or hand OA. For hip OA, the risk increases with age at about the same rate in women and men but it seems to progress more rapidly in women. Only a few studies provided data on spine disease, with no significant difference in risk between males and females for cervical or lumbar spine OA.

Among those < 55 years of age, no significant differences were found between genders for peripheral OA. A greater risk has been highlighted for cervical spine OA in males < 55 years of age, but not for other sites of spine disease.

Gender differences in OA severity were greater amongst individuals aged > 55 years. Severity in studies was classified using both the Kellgren and Lawrence scale and the self-reported outcomes. Knee OA was significantly more severe in females than males. On the other hand, there were no sex differences in the severity of hip and hand OA (Figure 1).

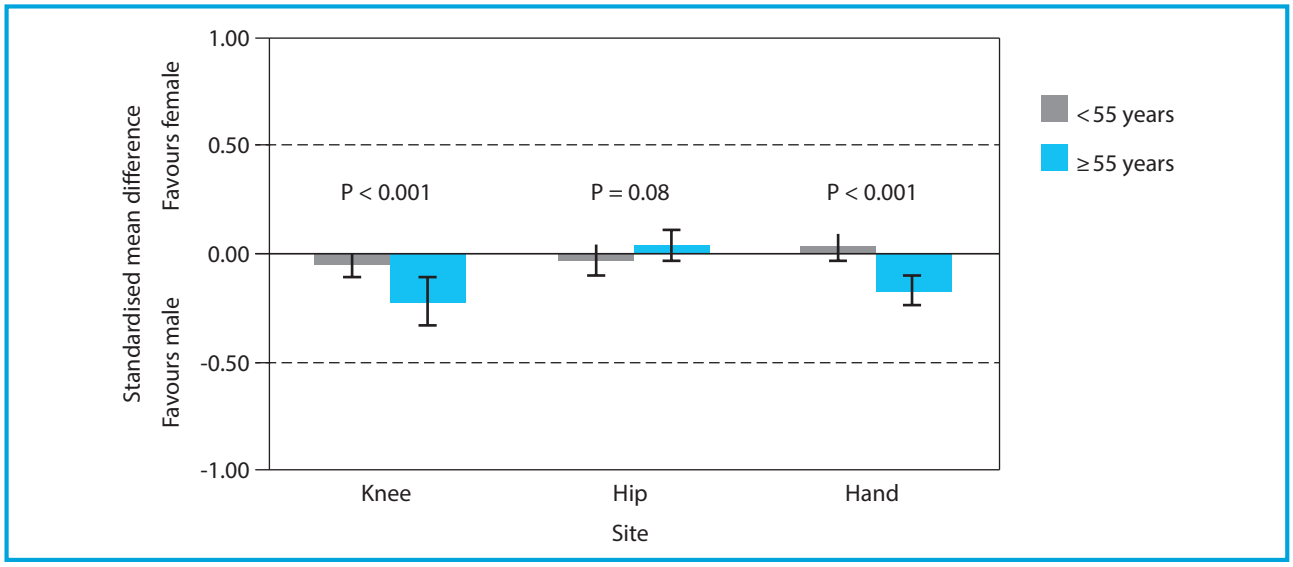

Figure 1. The effect of age on sex differences in severity of OA[43].

However, using a radiographic tool to define OA would seem to decrease the difference between genders compared to self-report or clinical methods. Indeed, non-radiographic approaches based on pain or other symptoms result in an overdiagnosis of OA. Greater pain levels in women may be mediated by specific behaviour leading to higher levels of self-report outcomes. Several studies show that symptomatic knee[5], hip[6] and hand OA[7] are all more prevalent in women. With regard to the incidence and progression of knee and hip OA, Murphy and colleagues estimated that the lifetime risk of developing symptomatic knee OA was about 40% in men and 47% in women, whereas the lifetime risk for symptomatic hip OA is 19% for men and 29% for women[8,9].

The incidence of hand OA over a 9-year follow-up period, was similar in women (34.6%) and men (33.7%), as demonstrated by Haugen and colleagues, but the majority of those women (96.4%) and men (91.4%) with hand OA at baseline showed progression during follow-up. Incident metacarpophalangeal and wrist OA were rare, but occurred more frequently and at an earlier age in men than in women. Erosive OA occurred mostly in patients with non-erosive hand OA at baseline and was more frequent in women (17.3%) than men (9.6%)[7]. Oliveria and colleagues[10] reported age and sex-standardised incidence rates of symptomatic hip and knee OA in a Massachusetts health maintenance organisation: the incidence rates of symptomatic hip and knee OA increase rapidly around the age of 50 and then levelled after the age of 70 (Figure 2). This study reported that the incidence rates for women ranged from a low of 0/100,000 person-years among those ages 20-29 to a high of 583/100,000 person-years among those patients aged 70-79. For men, the incidence rates ranged from a low of 0/100,000 person-years among those aged 20-29 to a high of 445/100,000 person-years among those aged 70-79. The incidence rates for knee OA in women ranged from a low of 0/100,000 person-years among those aged 20-29 to a high of 1082/100,000 person-years for those aged 70-79. For men, the incidence rate was 839/100,000 person-years among patients aged 70-79 (Figure 2).

Finally, epidemiological studies performed on autopsy findings, report that cartilage erosions, subchondral reactions and osteophytes are present in the knees of 60% of men and 70% of women who die in the seventh and eighth decades of life. Prevalence assessed from such studies tend to be higher than those from radiographic investigations, partly because mild pathological changes are not apparent in radiographs and also because pathological studies examine the entire joint surface.

To quantify prevalence, incidence and disease progression it is crucial to make a distinction between symptomatic and radiographic OA. Women usually have higher rates than men and a levelling occurs for both groups around the age of 80.

Risk factors

- Age is one of the strongest risk factors for OA of all joints. Increasing prevalence and incidence of OA with age is probably a result, after several years, of different risk factors and biological changes.
  After the age of 50 women more commonly develop hand, foot, and knee OA. Female gender serves to amplify the age-related increase in the risk of OA occurrence in the hand and knee and in multiple joints, also known as "generalised OA". By contrast,

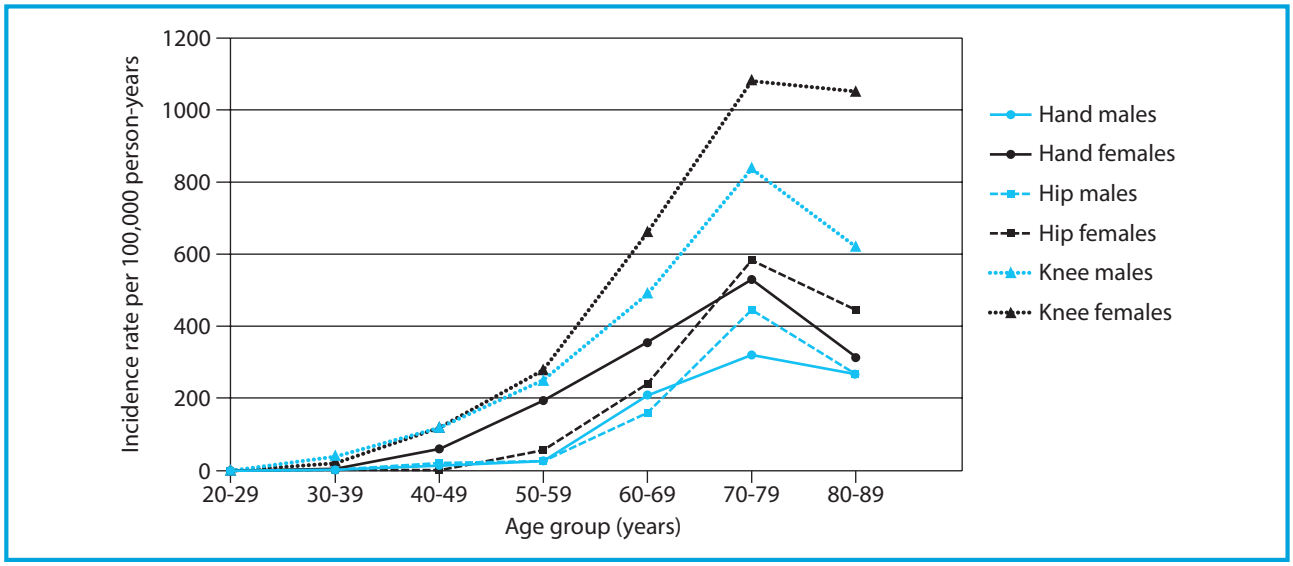

Figure 2. Incidence of OA of the hand, hip and knee in members of the Fallon Community Health Plan 1991-1992, by age and sex[10].

the frequency of hip OA increases with age at the same rate in women and men. However, hip OA appears to progress more quickly in women.

- Race/ethnicity: prevalence of OA also varies among racial and ethnic groups. Both hip and hand OA were less frequent among Chinese subjects in the Beijing Osteoarthritis Study than in Caucasian subjects in the Framingham Study[11,12]; however, Chinese women had a significantly higher prevalence of both radiographic and symptomatic knee OA than Caucasian women[12]. The prevalence of radiographic hip OA in Chinese subjects aged 60-89 years was 0.9% in women and 1.1% in men. Chinese women had a lower age-standardised prevalence of radiographic hip OA than Caucasian women. Chinese men had a lower prevalence of radiographic hip OA than Caucasian men of the same age[11]. Results from the Johnston County Osteoarthritis Project demonstrated that the prevalence of hip OA in Afro-American women (23%) was similar to that in Caucasian women (22%). In Afro-American men, the prevalence was slightly higher (21%) than in Caucasian men (17%)[13]. The Johnston County Osteoarthritis Project also reveals differences in radiographic OA patterns in Afro-Americans to Caucasians. For example, superior joint space narrowing and osteophytes in the lateral compartment are more common in Afro-Americans than in Caucasians and in men than in women[13]. Besides, Afro-American women are more likely to develop more severe tricompartmental osteophytes compared to Afro-American men[14].
- Mortality: patients with OA are at higher risk of death than the general population.
  Predictors of excess mortality, as shown in several studies, were diabetes, cardiovascular disease, cancer and the presence of walking disability. Conversely, little evidence suggests that age-standardised mortality ratios differ between men and women[15]. Possible explanations for the higher level of mortality include reduced levels of physical activity among OA patients, probably due to the involvement of lower limb joints and the presence of comorbid conditions, as well as the adverse effects of therapies commonly used to treat symptomatic OA, particularly non-steroidal anti-inflammatory drugs[16].
- Genetics: results from several studies have shown that OA is inherited and may vary according to joint site. Twin and family studies have estimated that the heritable component of OA is between 50% and 65%, with a broader genetic influences for hand and hip OA than for knee OA[17]. As genetic factors play an important role in hand OA, it remains to be seen whether the difference between sexes can be explained by interplay between genes and systemic or environmental factors[18]. Indeed, recent data indicate that epigenetics contributes to the pathogenesis of OA and it synergises with genetic predisposition to accelerate the onset and severity of disease[19]. The identification of OA loci confirmed that genetic risk shows joint-specific effects, with loci often contributing to disease risk at a specific skeletal site. Moreover, some loci are associated with OA in both males and females, whereas others are sex-specific, suggesting gender differences in the molecular mechanisms at the basis of OA susceptibility[20].
- Obesity and metabolic syndrome: obesity is among the strongest and best-established risk factors for knee OA. It precedes the development of knee OA by many years, and accelerates structural worsening of existing knee OA. On the contrary, weight loss has been associated with improved OA symptoms in a dose-response manner and with slower knee cartilage degeneration in two different studies[21,22]. The estimated prevalence of symptomatic knee OA was highest among adults aged 55 to 64 years and a study conducted by Losina and colleagues showed that obesity increases this risk with particular gender differences. The estimated prevalence of diagnosed symptomatic knee OA was 6.7% in non-obese males aged 55 to 64 years and 13% in obese males of the same age. In the female group, the estimated prevalence was 7.85% in non-obese patients and 18.94% in obese females aged 55 to 64 years[23]. As indicated by epidemiological studies regarding total hip replacement for OA, obesity is also a risk factor for hip OA. A prospective cohort study from Spain recently found an independent association between weight gain and hip OA[24]. Some studies also find an increased risk for hand OA in obese patients. Because hands are not load bearing joints, this highlights the role of systemic factors in the link between obesity and OA. The primary mechanism that could explain the development of OA in obese patients is likely to involve the effect of excess weight that overloads the joints, especially the hip and knee. Metabolic factors associated with obesity, including circulating adipokines or lipid abnormalities, beyond chronic inflammation, may also play a role in the pathogenesis of OA and could explain the modest association with obesity and hand OA. Elevated levels of blood glucose and C-reactive protein (CRP), which are often elevated in obesity, are associated with the risk of knee OA and its progression specially in women. Very few studies have investigated the relationship between hyperlipidaemia and OA. A recent case-control study from the United Kingdom demonstrated that hyperlipidaemia was an independent risk factor for new onset of hand OA[25]. Obesity is characterised by adipocyte hypertrophy. More leptin and less adiponectin are secreted,

whereby leptin accelerates and adiponectin inhibits the development of metabolic syndrome[26]. The leptin/adiponectin (L/A) ratio has been proposed as a new marker for the monitoring of metabolic disorders such as obesity, type 2 diabetes mellitus and hypertension[27]. A recent study by Selthofer-Relatić and colleagues[28] demonstrated that gender differences exist in leptin and adiponectin blood levels. Leptin levels were much higher in females than in males; also, the adiponectin levels were higher in the female group than in the male group. The L/A ratio was not related with BMI or weight measurements in either groups, but it was related with visceral-type obesity in females. This is probably due to hormone-related differences in body structure and the distribution of adipose tissue in men and women.

Phenotypes

OA is a multifaceted and evolving syndrome with great variability in clinical presentation and long-term disease prognosis. To better explain this heterogeneity, different phenotypes were recently characterised by the involvement of different structures at different degrees and different aetiologies. The expression of a given phenotype occurs in the early stages of the disease and ultimately hesitates in common clinical manifestations in late stages of the disease. A better characterisation of different OA subsets is crucial for an adequate stratification of patients during the course of the disease[29].

Pain and mental status

Women are more likely to self-report OA. Greater pain levels in women may be mediated by specific forms of behaviour that could lead to these differences compared with men.

Women show significantly higher pain scores, lower functioning and vitality scores. In addition to biological factors, psychosocial factors (such as depression, stress and fatigue) are associated with an increase in clinical pain and functional impairment[30].

Women commonly spend more of their time on unpaid work, such as housework or caring for children, which are associated with joint involvement, especially of the hands, due to the presence of greater manual tasks[31].

- Outcomes after intra-articular therapy: a recently published article evaluated gender differences in 1022 patients with hip OA who underwent intra-articular therapy. Values of a pain VAS, Lequesne index, NSAIDs intake and global medical and patient-reported assessments were evaluated from the baseline to the end of the follow-up, seven years later. Females showed a higher baseline level of pain, a higher Lequesne index score and higher NSAIDs consumption than men. Over time, the authors observed a progressively better response amongst males in all the composite indexes used than amongst women, who had a basically stable response[32].
- Opioid consumption: as a consequence of a greater pain sensitivity, women more likely report use of opioids than men. In accordance with findings from LeResche et al, women were more expected to report chronic health conditions such as pain and depression[33].
- Central sensitisation: different studies highlight sex disparities in pain sensitivity with women reporting lower pain sensitivity than men[34,35] and more chronic conditions that cause pain which are associated with painkiller use. Previous studies have also shown men to be less likely to seek help from their doctor[36]; this may explain why women are also more frequently prescribed and more frequently use prescription opioids[37]. Several studies have established that knee OA is significantly more severe in females. Although there were no significant sex differences in the severity of hip and hand OA. Traditionally, knee OA is considered as a condition of peripheral pain. However, given that radiological findings of joint damage do not correlate with the degree of clinical symptoms and often women experience greater pain and disability than men, other centrally-mediated factors have been supposed to influence this condition[38-40]. Bartley et al[41] found that central sensitisation helps to enhance pain in women with knee OA. Indeed, women show greater sensitivity to a number of different stimuli, including greater temporal summation, heightened sensitivity to multiple pain modalities, greater number of pain sites. Therefore, the female sex may be a moderator of centrally-mediated changes in knee OA pain[42,43].

Outcomes in prosthetic surgery

Total joint replacement (TJR) is a noteworthy successful treatment for OA, resulting in pain relief and improvement in joint function. However, considerable gender disparities exist in its use and in the results provided. Investigations have revealed that women develop more severe symptoms, have greater impairment and are at a more advanced stage in the course of disease than men at the time of surgery. Besides, pain and functional improvement after both primary and revision TJR are more advantageous for men[44,45]. Some studies highlight that women report more post-operative pain, more intense

pain overall and reduced daily activities for pain, compared to men. Whether this difference is due to real differences in physical response to pain, or due to delays in treatment, or due to the influence of social and behavioural factors (for example, men are supposed to tolerate pain better than women) is unknown[46,47]. Women express more concern than men regarding anaesthesia, pain management, and recovery after TJR. Also, women are more inclined to accept a slow functional decline rather than accept the risks of a surgery procedure. Other possibilities may include caregiver status[48]. Sex disparities also exist in differential access to the healthcare system between women and men. Investigations have revealed that women are less likely than men to see an orthopaedic surgeon as well as undergo a TJR. Furthermore, women were less likely to be recommended by their physicians for TJA and consequently have lower rates of replacement surgery than men. Possible reasons for this difference could involve the primary care physician's point of view regarding risks, indications and expected outcomes of TJR that makes women less appropriate candidates for surgery than men[49]. All these factors might contribute to sex differences in getting surgical consultations beyond TJR[50,51].

Conclusions

Data from literature seems to show that sex differences exist in the presence or intensity of pain, in radiographic progression and in behavioural response to pain and consequent physical disability.

Although slight differences exist in particular aspects of the disease, such as epidemiology, risk factors, pain status and prosthetic outcomes, these are important to understand the specific impact of sex on the development and progression of disease with the final purpose of obtaining the best treatment strategy for each patients according to personal and peculiar characteristics.

Indeed, gender medicine, one of the most promising topics of individualised and precision medicine, analyses the specific impact of gender on the development and evolution of diseases. Understanding the pathogenic mechanisms underlying sex differences in OA will help to develop targeted treatments to provide a better quality of life and delay joint failure due to disabling OA.

Further studies on gender differences in care needs, treatment effectiveness, comorbidity related disability and disease progression, are needed.

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Key messages

- OA is a composite and heterogeneous syndrome rather than a single disease.
- Gender disparities can be partially explained by the complex interplay between genes and systemic or environmental factors.
- Women show more severe symptoms, a greater disability and a more advanced stage.
- A better response after total joint arthroplasty has been observed in men.
- Gender differences in OA severity are greater amongst individuals older than 55 years.

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