# Handbook of Clinical Gender Medicine

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# Osteoarthritis

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**Abstract**

Osteoarthritis (OA) is a joint condition that is characterized by loss of articular cartilage, the formation of osteophytes, and sclerotic and cystic changes in local bone. There are male-female differences in the prevalence, location, and severity of OA. Further, women are more likely to report OA-associated pain as compared to men but are less likely to utilize surgical interventions for OA treatment. This sexual dimorphism with respect to OA may be related to anatomical differences in the boney structure of male and female skeletons, differences in the amount and composition of cartilage volume, differences in body typology and fat distribution patterns in men as compared to women, or the impact of sex steroid hormones on the pathophysiology of OA. Recognition of the male and female differences in OA may have important ramifications for prevention and treatment and may inform hypotheses about disease onset and progression. 

Osteoarthritis (OA) is a multifactorial disease process whereby progressive musculoskeletal pain and limitation in movement are accompanied by the loss of articular cartilage, sclerotic and cystic changes in local bone, and osteophyte formation. OA is a joint condition whose presentation so differs between men and women in its attributes that both prevention activities and treatment would benefit by recognition of this dimorphism. This is particularly relevant as OA is a highly prevalent disease whose impact is expected to increase as the number and proportion of the population of the USA and the world over the age of 60 years rises and the number of men and women with excess body weight becomes increasingly common [1].

## Epidemiology, Diagnosis, and Clinical Features

*Sexual Dimorphism in Osteoarthritis Prevalence Estimates Based on Joint Imaging*

In the relatively few studies of OA that include men and women in community-based or population-based samples, there is strong evidence of sexual dimorphism. In the period between 1950 and the 1980s, differences were identified in the prevalence,

location, and severity of OA in: the UK; an NHANES sample representative of the noninstitutionalized adult US population; adults in Tecumseh, Mich., USA, and adults in New Haven, Conn., USA. In these studies, women had more multiple joint involvement and involvement in the hands, knees, ankles, and feet [2]. Men had a greater prevalence of OA of the hips, wrist, and spine.

More recent studies that also include non-Caucasian populations further indicate that female gender is a major predisposing factor of knee OA and is associated with more severe clinical manifestations than in men. In NHANES III, a sample representative of the US population, those individuals with knee OA (radiographic definition of Kellgren-Lawrence grade ≥2) over 60 years of age were more likely to be female and non-Hispanic blacks in comparison to those without knee OA. In a study of 660 Korean community residents aged 65–91 years, women had more severe symptom progression between Kellgren-Lawrence grades 2 and 3 and grades 3 and 4 than did men. Furthermore, women had worse mean WOMAC and SF-36 scores (indicating more diminished physical functioning) than men with the same radiographic grade of knee OA. Notably, BMI was similar in Korean men and women (BMI ~24 kg/m$^2$). In Japanese patients aged 60–69 years, the prevalence of radiographic knee OA was 57% in women and 35% in men [3].

Hip OA in women may be related more often to a systemic disease and this systemic disease may be a more rapidly progressing form of the disease whatever its location. In the ECHODIAH study to test the efficacy of diacerin, an inhibitor of IL-1β, in OA, hip OA in women was more frequently part of a polyarticular OA and displayed greater symptomatic and structural severity [4].

*Sexual Dimorphism in Joint Conformation*

The boney structure around the knee is different in men and women. The female femur is narrower than the male femur. Women have a thinner patella, a slightly larger quadriceps angle (Q angle), and a smaller lateral tibial condyle relative to the medial tibial condyle [5].

These structural and anatomic differences between the sexes are observed in both early and later life. Articular cartilage of the distal femur is less thick in girls and women as compared to boys and men. In young people 8–18 years of age, boys have significantly more knee cartilage than do girls, even following statistical adjustment for age and physical activity. As characterized by MRI, adult men have significantly larger patellar and femoral cartilage volume than women, independent of body and bone size [6]. In a follow-up evaluation, women had substantially higher knee cartilage loss than men; these sex differences were discernible at age 40 and became more pronounced with increasing age. In general, the distal femurs of females are not only smaller but also have different shapes with a narrower medial-lateral diameter for any given anteroposterior distance compared to males [5].

The anatomic differences in knee and hip joints translate into differences in how these joints contribute to mobility in male and female gait patterns. In an

Israeli study of gait among men and women with knee OA, males and females walked at the same walking speed, cadence, and step length, but there were significant differences in the gait cycle phases. Males walked with a smaller stance and double limb support and with a larger swing and single limb support compared to females. In addition, males walked with a greater toe-out angle compared to females [7].

*Sex Dimorphism and Osteoarthritis Biomarkers of Connective Tissue Activity*

The use of OA biomarkers related to connective tissues (i.e. hyaluronic acid) has not shown the sex dimorphism in OA that has been observed with imaging, implementation of functioning measures, and pain assessment. Cartilage oligomeric matrix protein (COMP) is a glycoprotein that is found predominantly in cartilage but is also present in ligaments, tendons, menisci, and the synovium. Serum hyaluronan (HA) has also been proposed as a potential biomarker of OA. Local increased production of HA has been demonstrated in inflamed synovium from patients with OA and reactive arthritis. It is well recognized that, although HA is concentrated in connective tissue, it is widely distributed in the body and that levels of serum HA can be influenced by conditions including liver disease, impaired renal function, hypothyroidism, and rheumatoid arthritis. However, some investigators have posited that biomarker levels for disease must be interpreted within context of the levels of sex-specific normal levels. For example, in evaluating 'normals' in each age group, the serum values of the metalloproteinase MMP-3 were always 2 times higher in males than in females, suggesting the importance of using age- and sex-matched normative data in employing these markers to evaluate patients with joint disease [8].

*Sexual Dimorphism and Musculoskeletal Pain, Functioning, and Injury*

Knee pain tends to be more frequently reported by women than by men. In the (1992–1993) Framingham Study, 63% of older women reported musculoskeletal pain compared to 52% of men. Widespread pain was more prevalent among women than men (15 vs. 5%, respectively). Older men and women differed in the factors associated with musculoskeletal pain. Factors associated with pain only in women included BMI, systolic blood pressure, and depressive symptoms. In men, but not women, pain was associated with polyarticular radiographic OA. In a Swedish population registry, among people aged 55–74 years, women reported significantly more knee-related complaints on the Osteoarthritis Outcome Score (KOOS) *Pain, Symptoms,* and *ADL* functioning subscales than age-matched men. There was a marked offset by age group. Among men, worse *ADL* and *Sport and Recreation* functioning was seen in the 75- to 84-year age group compared to the younger age groups. However, worse *Pain*, *ADL*, *Sport and Recreation,* and *QOL* were already seen in women 55–74 years of age compared to the younger age groups [9]. OA prevalence and characteristics by gender are shown in table 1.

**Table 1.** OA, OA sequelae, and joint characteristics according to gender

| | Women | Men |
|---|---|---|
| OA prevalence by radiograph | About 30% higher | |
| OA location | Multiple joints, knees, hand, ankles, feet | Hips, spine |
| Pain | About 15–25% higher | |
| Decrements in function and quality of life | Occurs about 10 years before occurring in men | |
| Gait cycle differences | | Smaller stance, larger swing, greater toe-out angle |
| Connective tissue biomarkers | No reported difference | |
| Boney structures | Smaller | Larger |
| Articular cartilage thickness | Thinner | Thicker |
| Cartilage volume (independent of bone and body size) from childhood | Less | More |
| Bone mineral density | Lower | |

While the risk for knee OA following anterior cruciate ligament (ACL) disruption is well established, regardless of sex, women are proportionately at a higher risk for ACL injury. It is estimated that adolescent and young adult women are 8 times more likely to experience an ACL tear than similarly aged young men, when standardized to the amount of time playing sports. The sequelae of these injuries are troubling. An isolated ACL tear will increase the risk of OA 10-fold, whether treated operatively or nonoperatively. A significant percentage of ACL reconstructions with reasonable joint stability develop degenerative changes within a relatively short time, including 70% developing radiological evidence of OA within 7 years. Consequently, even if ACL reconstructions produce normal kinematics at the knee, the concomitant injuries to the menisci, hyaline cartilage, and secondary restraints are believed to generate early degenerative joint changes over time [10].

Some studies have identified that a preponderance of ACL injuries in women occurs in the periovulatory phase of the menstrual cycle rather than being equally distributed across the entire menstrual cycle, as could be expected. Because hormones affect the neuromuscular and musculoskeletal systems and represent one of the most basic differences between males and females, it is logical to question whether the female endocrine cycle or its metabolites, and the response to athletic training and conditioning, affects knee protective mechanisms and/or collagen balance in ways that could contribute to ACL injuries. This hypothesis awaits verification.

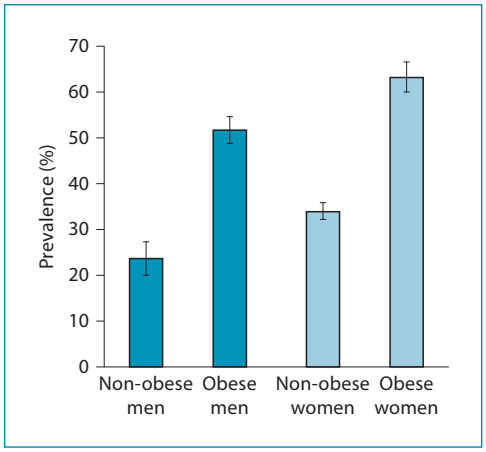


**Fig. 1.** Prevalence (95% CI) of knee OA by obesity status and gender among an NHANES III sample of older adults.

## Pathogenesis

*Sexual Dimorphism and Risk Factors for Osteoarthritis: Obesity*

Obesity has long been considered the major risk factor for OA, particularly knee OA (fig. 1). In NHANES III, the average BMI among those with knee OA was 29.4 compared to 26.0 among those without knee OA ($p < 0.0001$). While one fourth of the total sample (25.3%) was classified as obese (BMI ≥30), 40% of those with knee OA were classified as obese.

A recent review by Sowers and Karvonen-Gutierrez [1] examined the literature with respect to the different mechanisms by which obesity can influence OA onset and progression. Some investigations have found that the sheer mechanical force exerted by obesity leads to increased joint loading and subsequent damage to the articular cartilage. Clinical and animal studies of joint loading have provided evidence that abnormal loads can lead to changes in the composition, structure, and mechanical properties of articular cartilage. Biomechanically, muscle forces are a major determinant of how loads are distributed across a joint surface. Decreasing the muscle forces acting around a joint or malaligned joints will ultimately alter loading conditions. Failure by the quadriceps to adequately absorb forces about the knee can cause greater dynamic loads being placed on the articular cartilage, resulting in progressive degeneration. As a result, quadriceps weakness has been shown to be an important risk factor for OA in some but not all studies.

The role of biomechanical loading attributable to obesity does not explain the associations observed between obesity and OA in non-weight-bearing joints, thereby motivating additional and alternative explanations for the OA-obesity relationship. Evidence for the importance of adipose tissue to the metabolic environment of the joint has prompted hypotheses about the relationship of obesity and OA that extends beyond those of biomechanical loading.

*Sexual Dimorphism, Obesity, and Metabolic Components*

Historically, inflammation and inflammatory diseases have been recognized as being sexually dimorphic. It is clear that that the treatment of OA must address the contribution of both the inflammatory response and/or obesity, both of which have a dimorphic element.

Emerging evidence reviewed by Katz et al. [11] demonstrates that chondrocytes have an active metabolic environment characterized by glucose transport, cholesterol efflux, and lipid metabolism. These findings have led investigators to consider biomarkers that may reflect an underlying pathology between OA and the cardiovascular and metabolic diseases. Associations between C-reactive protein, a biomarker of chronic inflammatory response, and knee OA prevalence and incidence have been reported in some but not all studies. Further, relationships between individual cardiovascular or metabolic risk factors and OA are mixed. While some studies have found positive associations between knee OA or hand/wrist OA with cardiovascular risk factors including uric acid, cholesterol, or hypertension, these findings are not consistent across studies.

It is well reported in the literature that a sexual dimorphism with respect to body composition exists, suggesting that fatness may mean something different for males versus females. For a given level of BMI, women generally have a larger proportion of body mass that is fat as compared to men. Fat distribution differs between men and women; men are more likely to deposit fat viscerally whereas women are more likely to deposit adipose tissue subcutaneously. This sexual dimorphism in body composition and body topology may offer some clues with respect to the sexual dimorphism observed in OA.

Population studies of OA and obesity in men and women have rarely incorporated measures of obesity-related inflammation, obesity-related insulin resistance measures, or markers of fat tissue metabolism such as leptin, an adipocytokine that is an important modulator of the inflammatory response. The synthesis and secretion of leptin has been demonstrated in osteoblasts and chondrocytes and its receptors have been identified in articular cartilage. In a preliminary examination of data from the NHANES III population, striking sex differences were observed for HOMA-IR (homeostatic model assessment of insulin resistance, a proxy indicative of insulin resistance) and leptin in relation to having knee OA. In models that were stratified by obesity status and sex, the relationship between logHOMA-IR was most strongly associated with knee OA among men. Conversely, among women, leptin levels were most important with respect to knee OA [Karvonen-Gutierrez, pers. commun.].

The preliminary findings of a sex dimorphism in the relationship of knee OA to leptin and insulin resistance may reflect the predominance of each factor as the more important obesity-related hormone for that sex, reflecting differences in fat deposition patterns. Leptin levels correlate better with the amount of subcutaneous adipose tissue, which is proportionally larger in women, whereas insulin levels are better

**Table 2.** Risk factor characteristics according to gender

| | Women | Men |
|---|---|---|
| Obesity | Occurs about 30% more frequently than in men | |
| Fat mass/unit of BMI | Greater | |
| Visceral obesity location | | Insulin resistance |
| Subcutaneous obesity location | Inflammation | |
| Sex hormone responsiveness | Controversial findings | |

**Table 3.** Intervention and treatment

| | Occurrence |
|---|---|
| Delay of surgery until a more advanced stage | More often in women |
| Use of 'sized' implants | More often in women |
| Consideration of implications of greater depressive symptoms | More often in women |
| Consideration of social support during recovery | More often in women |

correlated with the amount of visceral adipose tissue, which is proportionally larger in men. This hypothesis is further supported by evidence of a sexual dimorphism in animal models where the brains of male rats are more sensitive to insulin but female rats are more sensitive to leptin. Furthermore, leptin levels in women are higher for a given amount of fat mass, but increases in body fat among women are associated with smaller decreases in insulin sensitivity as compared to men. Risk factor characteristics by gender are shown in table 2.

*Sex Hormones and Osteoarthritis*

A continuing suggestion in the attempt to explain sexual dimorphism in OA is the possibility of joint tissue sensitivity to hormones, and particularly estrogen. Estrogen receptor (ER)-α and ER-β have been identified; however, the processes by which estrogen might modulate chondrocyte behavior remain poorly understood. An example of the conundrum is reflected in the earliest report of ER gene expression. The responses to the reproductive hormones in animal models have been model specific. ER-α and ER-β receptors are present in rat growth plate chondrocytes but female cells have more high affinity receptors than do male cells. Female rat cells had decreased proliferation and increased alkaline phosphatase activity relative to male rat cells.

Clinical studies of hormone therapy have been inconsistent in showing a relation between serum estradiol levels and development or progression of OA. Further, studies of hormones in human populations have consistently recognized that, because bone tissue is a component of the total joint, it is challenging to identify if associations with the sex hormone tissues are related to bone or other joint elements including connective tissue, cartilage, and endothelial lining tissues like synovia.

## Treatment

*Implications for the Role of Sexual Dimorphism in Arthroplasty and Joint Replacement*

It has been estimated that, while surgery for severe hip and knee OA is underused by both men and women, the degree of underuse is estimated to be approximately three times greater in women compared to men. Reports demonstrate that, in general, women tend to delay surgery for their arthritic knees and may wait until their symptoms are more severe as compared to men [12]. Age, gender, and obesity influence joint replacement success. The best results were seen in nonobese women over 60 years of age whose survival at 10 years was 99.4%. The worst results were in obese men with OA who were less than 60 years old and who had a survival at 10 years of 35.7%, whereas the nonobese men with OA aged less than 60 years had a survival at 10 years of 92.7%. 66% of all patients whose total knee replacement (TKR) failed had a BMI which was in the obese category.

In view of findings of worse preoperative scores in women than in men, investigators have suggested that this situation may be based in part on delay in seeking care, because women are often primary caregivers and have less social support and a higher incidence of obesity [13]. Women and men may have comparable improvement in their postoperative function scores, but the scores in women remain worse than those in men potentially because of the significant preoperative differences. Further, a higher incidence of poorer emotional health and depression before TKR in women could be detrimental to the outcome after TKR.

The importance of sex differences in knee anatomy has been acknowledged with the development and use of knee arthroplasty components designed for women. The gender-specific components are designed to better accommodate the anatomic differences in females who typically have a narrower medial-lateral dimension for any given anteroposterior dimension. Additionally, the angle of the trochlear groove is increased and the anterior flange thickness is reduced to better match the native female anatomy. Surgical procedures also exist in which there is size matching of the implant to patient bone with ongoing work to optimize this match [14]. Furthermore, as work continues on new methodologies for OA treatment, such as cartilage implants, investigators have identified that sexual dimorphism (female vs. male rat tissues) influences the muscle-derived stem cell chondrogenic differentiation for articular cartilage regeneration [15].

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