

On the Horizon From the ORS

Sex Differences in Osteoarthritis of the Knee

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Osteoarthritis (OA) is a leading cause of disability in the United States. It is the most common form of arthritis and afflicts 13.9% of adults aged ≥ 25 years and 33.6% (12.4 million) of those aged >65 years—an estimated 26.9 million persons in the United States.¹ Studies sponsored by the Centers for Disease Control and Prevention and the National Institutes of Health have identified differences in the incidence and severity of OA between men and women, as well as between racial and ethnic groups.^{2,3}

The burden of OA is highest among women and African-Americans, who disproportionately develop knee and hand but not hip OA. The disproportionate number of women in the aging US population is of clinical concern because of the more severe knee OA and its impact on quality of life and independence.

Based on these factors, there is a need for research focused on the effect sex differences have in the development and progression of OA as well as the impact on prevention and treatment strategies. However, most studies on the mechanisms underlying OA have not taken sex differences into account, whether in vitro cell culture or animal models were used. Although little is known about the mechanisms that contribute to disparities between men and women in disease incidence and severity, they likely involve mechanical and molecular events in the affected joint.

Diagnosis of knee OA is based on evidence of joint pain and/or reduced space between articulating bone surfaces as a result of thinning of the opposing articular cartilages. However, multiple tissues that compose the knee joint appear to be compromised

by the disease, including subchondral bone, articular cartilage, the meniscus, the anterior cruciate ligament, the synovium, and synovial fluid. A change in any of these tissues can influence the distribution of load across the joint, with corresponding adaptations in the other tissues and, ultimately, the cartilages. Such pathophysiologic changes may exacerbate age-related physiologic changes in joint function attributable to genetic characteristics, age, sex, and health status, leading to greater cartilage damage.

To understand the expression of knee OA in males and females, it is important to view the knee as an organ rather than focusing only on the articular cartilage. Knee tissues are modulated by sex hormones during tissue development and throughout the life cycle in both males and females. Although menopause is associated with an increase in OA severity in women, systemic estrogen alone cannot explain the observed sex differences. Recent data, for example, show that sex-specific variations in the responses of chondrocytes to sex steroids are the result of differences in receptor number as well as mechanisms of hormone action.⁴

In addition to increased prevalence of knee OA, women often have greater pain and more substantial reduction in function and quality of life than do men.⁵ OA pain can be related to the sensory information that emerges from the knee joint. The pain does not always match the degree of injury, however, and can continue even after total joint arthroplasty. The neural and other mechanisms underlying these differences in pain between men and

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women with knee OA are unknown. By improving our understanding of the mechanisms responsible for sex differences in the perception of pain in OA, more effective and, possibly, sex-specific treatment strategies will emerge.

Although the adaptations that accompany advancing age may be a major factor in its etiology in older patients, early-onset OA is becoming more common. Women with physically active lifestyles, such as athletes and workers in occupations that involve exposure to traumatic injury or to mechanical stress, are more subject to early onset OA. Anterior cruciate ligament injuries are particularly problematic in 16- to 20-year-old females. Approximately 50% of these young women will progress to OA in 10 to 15 years.^{6,7}

The prevalence of obesity in children and young adults is escalating, and the impact of increased mechanical stress

on the knee during bone growth and development is not yet fully understood. In addition, the role of sex differences, particularly hormonal regulation, and its influence on the onset and progression of OA is not yet known.

In summary, epidemiologic studies have established that sex differences exist in the incidence and severity of knee OA. Therapeutic approaches to the management of OA, particularly regenerative medicine strategies, have not yet taken these sex differences into consideration. Effective interventions, however, will require a better understanding of the mechanisms involved in the disease and its differential expression in men and women.

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