

Osteoarthritis in Menopause

Ann K. Rosenthal, MD

Osteoarthritis is the most common form of arthritis in adults and affects millions of older Americans.¹ It is characterized by radiographic and functional deterioration of joints. Loss of articular cartilage is perhaps the best-recognized feature of osteoarthritis, but involvement of bones, tendons, ligaments and muscles also commonly occurs.

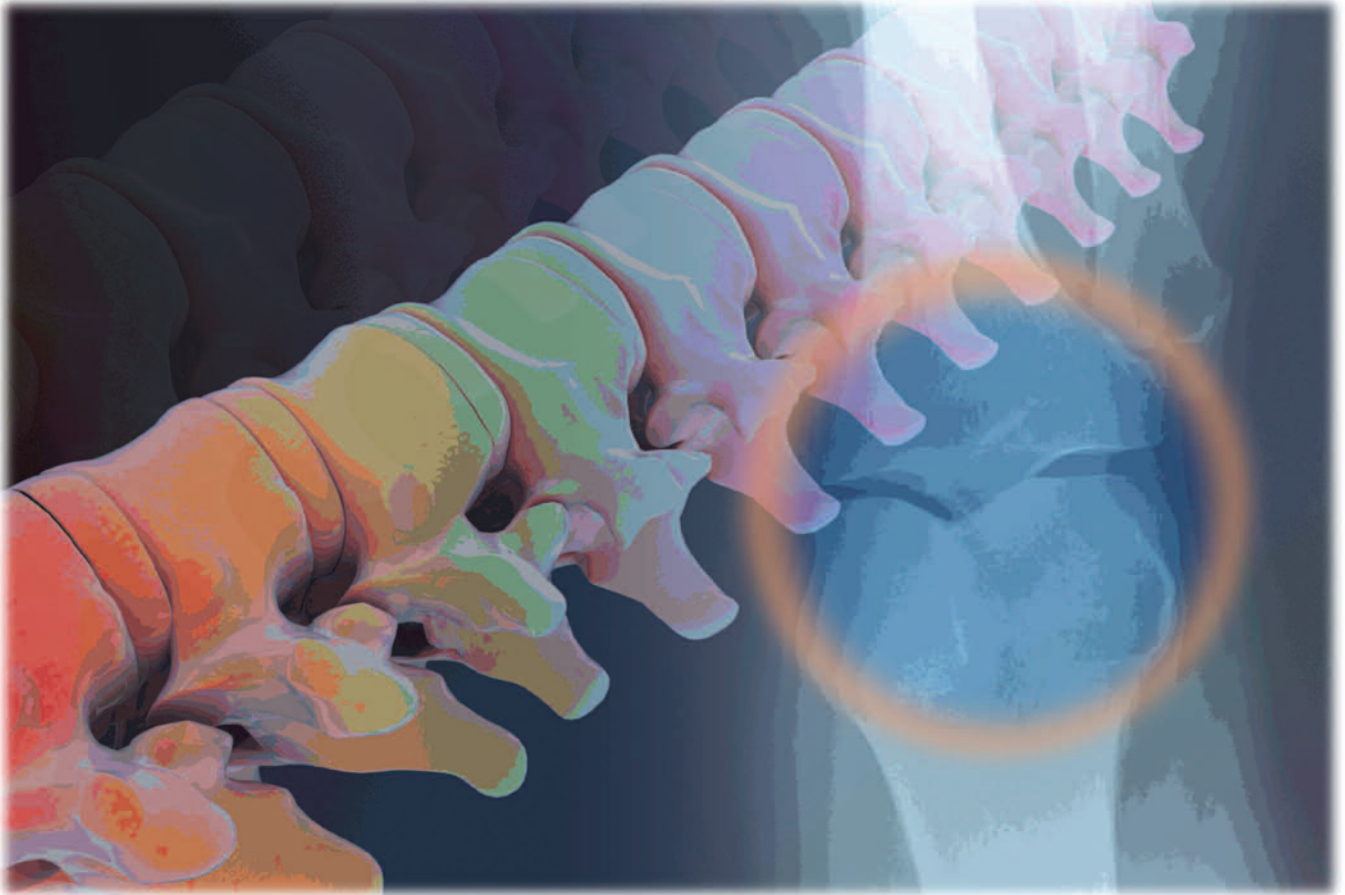
Osteoarthritis is defined radiographically by a constellation of features, including loss of joint space, the presence of bony spurs known as osteophytes, sclerosis of the subchondral bone and bony cyst formation. Clinically, these radiographic findings are associated with joint pain and stiffness in many patients. Osteoarthritis typically involves large weight-bearing joints (such as the knee and hip), small joints (including the distal and proximal interphalangeal joints, the base of the thumb, and the big toe), and the cervical and lumbar spines. Patients complain of pain that is often worse at the end of the day and after activity. They frequently describe several minutes of stiffness or pain upon arising in the morning or after periods of immobility. The latter symptom is termed *gelling*. Soft tissue swelling is rare, and more often bony deformities are noted. Large joint effusions can occur.

Etiology

The causes of osteoarthritis are clearly multiple, and this disease likely represents a final common pathway resulting from an accumulation of small and large insults. Osteoarthritis can be inherited, and runs through maternal bloodlines in its generalized form. Generalized osteoarthritis, which affects both large and small joints and typically involves the hands, is also known as primary nodal osteoarthritis (Figure, page 22). Other risk factors for osteoarthritis include obesity, joint injury, mechanical misalignment and congenital anomalies such as acetabular dysplasia.

Enigmatic Features

While osteoarthritis is typically easily diagnosed, some features remain enigmatic. For example, there is often little correlation between the radiographic grade of disease and the severity or presence of joint pain. Some patients have very severe pain with minimal x-ray changes, while others have moderate or severe radiographic osteoarthritis and remain completely asymptomatic.



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Thus, the origin of pain in osteoarthritis remains complex.

This dissociation between symptoms and apparent structural changes presents a significant therapeutic challenge. Will treatments that prevent or ameliorate cartilage loss also help with pain and stiffness? Second, while risk factors for developing osteoarthritis are well-defined, those that predict progression are less well understood. The natural history of osteoarthritis is quite variable. Some patients rapidly develop severe disease, while others maintain their current status for many years. These issues have major ramifications for interpreting findings from both epidemiologic studies and therapeutic trials related to osteoarthritis.

Estrogen, Other Sex Hormones and HT

The role of estrogen and other sex hormones in osteoarthritis has been a longstanding theme in osteoarthritis research.²⁻⁴ A putative role for sex hormones stems from several observations. Symptomatic osteoarthritis is clearly more common in women than in men, with most studies showing a ratio of three affected women for every one to two affected men.⁵ Osteoarthritis often begins around the time of menopause, and rates of involvement rise faster in menopausal women than in similarly aged men.⁶ Joint pain is a well-described and common complaint at the time of menopause⁷ or hormone therapy (HT) withdrawal.⁸ Indeed, some studies suggest that musculoskeletal symptoms are more commonly associated with menopause than are hot flashes.⁹

These observations largely support the hypothesis that estrogen

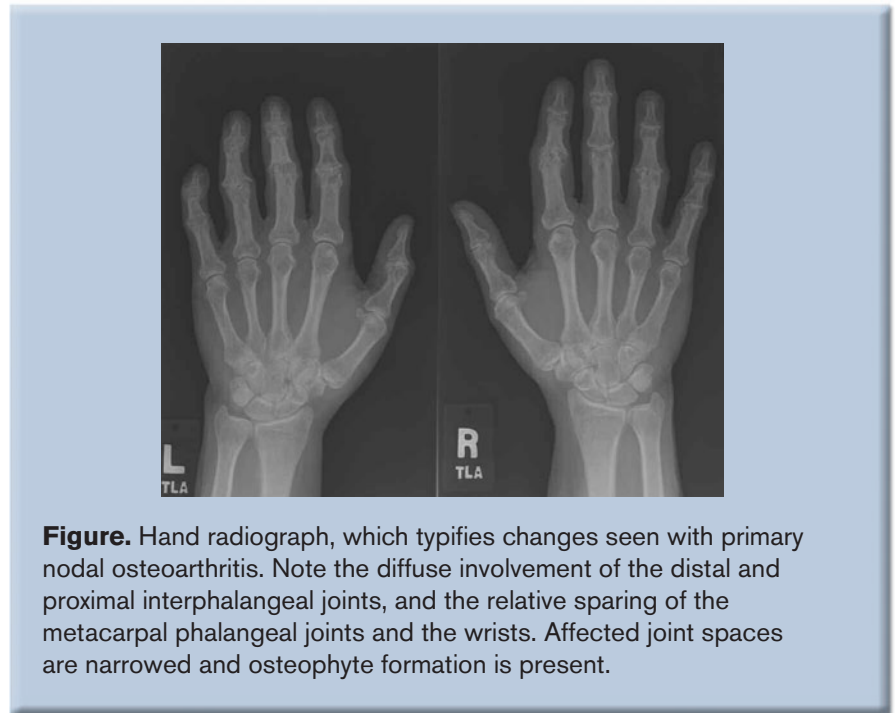


Figure. Hand radiograph, which typifies changes seen with primary nodal osteoarthritis. Note the diffuse involvement of the distal and proximal interphalangeal joints, and the relative sparing of the metacarpal phalangeal joints and the wrists. Affected joint spaces are narrowed and osteophyte formation is present.

protects against osteoarthritis. According to this theory, a decline in estrogen levels during menopause, or after discontinuation of HT, would account for the high rate of symptomatic disease during this time. An alternative and considerably less popular hypothesis is that high estrogen levels—such as those seen in obesity—may actually contribute to osteoarthritis, which then simply becomes increasingly clinically apparent with age. Both of these hypotheses have been investigated in epidemiologic studies as well as animal studies and therapeutic trials. Although a consensus as to the role of estrogen and other hormones in osteoarthritis has not yet been reached, this work merits review.

If estrogen or other sex hormones contribute to osteoarthritis, then levels of these hormones should correlate with the presence of disease. A handful of studies have reported sex hormone levels in osteoarthritis patients. Few studies have found any

consistent trends in hormone levels in postmenopausal women,¹⁰ even when levels of sex-hormone binding globulins, estradiol, testosterone or dihydroepiandrosterone have been examined.⁴ A few small studies cite an increased rate of hysterectomy in patients with osteoarthritis,¹¹ while more recent work suggests no clear relationship.¹² Several attempts have been made to correlate genetic factors associated with sex hormones to osteoarthritis in women. For example, polymorphisms at the estrogen receptor α locus were associated with the development of osteoarthritis in a Japanese population with primary generalized osteoarthritis. However, these results were not replicated in a study of Caucasian women.¹³

If the development of osteoarthritis is related to hormonal changes around menopause, then HT should delay its onset or lessen its severity. While no randomized, controlled trials directly address this

issue, many of the large HT studies have examined osteoarthritis as a secondary outcome. Again, the evidence is conflicting. Taken as a whole, these studies suggest that while HT may modestly slow the structural progression of osteoarthritis, particularly in the hips and knees, it has no consistent effect on symptomatic osteoarthritis.²⁻⁴ In one study,¹⁴ the relative risk of osteoarthritis in women who were ever-users of HT compared with never-users was 0.73 (95% CI, 0.69-0.78). Carbone et al showed a reduction in bone marrow edema and subchondral bone attrition in woman taking HT, but no effect on knee pain.¹⁵ Thus, while HT appears to offer some slight protection against the development of osteoarthritis, its effect is not large and its use is not warranted for this purpose.

Unfortunately, animal studies undertaken to clarify these important issues have only further muddied the waters. Studies in primates and rats showed that systemic estrogen therapy may promote cartilage maintenance and repair while suppressing cartilage turnover.^{3,16} However, intra-articular administration of estrogen increased cartilage damage.⁴ When chondrocytes in culture are exposed to estrogen, cartilage matrix production may be stimulated. The mechanism of this effect is uncertain, but estradiol may protect against free radical damage.¹⁷ The presence of estrogen receptors on chondrocytes is well documented.^{17,18} Interestingly, estrogen receptors are present in both male and female cartilage. Estrogen receptor levels in one study were higher in male than in female carti-

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lage samples, but other studies have shown altered affinity for the estrogen ligand in males and females, and there is some evidence that the response to estrogen varies in chondrocytes from different sexes.¹⁸

It is possible that cartilage is not the target tissue for estrogen in osteoarthritis. Tendons, ligaments and muscles also play a role in this disease. One study examined ligament strength in ovariectomized rabbits.¹⁹ After treatment with estrogen, the strength of the anterior cruciate ligament was significantly reduced compared with the untreated controls. Thus, ligaments responsible for joint integrity may be weakened by estrogen and this may contribute to joint instability, injury and subsequent osteoarthritis. Similar hypotheses have centered on the role of bone in osteoarthritis. It has been postulated that stiffer or denser bones increase the load on articular cartilage and may lead to joint damage. This is supported by the observation that osteoporosis seems to protect against the development of osteoarthritis in population-based studies.⁴ If this hypothesis

is true, later menopause, HT and obesity might worsen osteoarthritis by increasing bone density.

Diagnosis

The diagnosis of osteoarthritis can generally be made by history and physical examination. Diagnosis is confirmed by x-ray and, when appropriate, examination of the synovial fluid can be done to rule out other pathology. In its classic form, osteoarthritis is not difficult to diagnose but must be differentiated from other forms of arthritis, such as gout, pseudogout, rheumatoid arthritis and mechanical derangement. It can be differentiated from inflammatory types of arthritis, such as rheumatoid arthritis, with a careful history. For example, the presence of morning stiffness lasting longer than 30 minutes, pain that improves as the day progresses and with exercise, and accompanying constitutional complaints such as weight loss or malaise, are classic features of inflammatory arthritis, and should not be present in a patient with osteoarthritis.

If the history or exam is not typical for osteoarthritis, obtaining a synovial fluid analysis and/or testing blood for inflammatory markers is often sufficient to rule out other diagnoses. If concerns about the diagnosis still persist, a rheumatology referral would be warranted. Otherwise, the primary care physician can often confirm the diagnosis and initiate therapy.

Treatment Recommendations

The conflicting results of the diverse body of studies on sex hormones and osteoarthritis contribute little to

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our current recommendations for patients. It is safe to say that there is no good rationale for HT after menopause in terms of either preventing or minimizing clinically significant osteoarthritis.

What do we tell patients about avoiding osteoarthritis? Because nothing can be done about our genetic makeup, the most modifiable risk factors are body weight and activity. Maintaining an ideal body weight and keeping the muscles and ligaments around joints strong may go a long way toward preventing the development of symptomatic osteoarthritis. It is unknown whether supplements such as glucosamine and/or chondroitin sulfate prevent disease.

Once symptomatic disease occurs, treatment options include both pharmacologic and nonpharmacologic modalities. Nonpharmacologic interventions, such as physical therapy and bracing, may improve symptoms and increase functioning for many patients with osteoarthritis. These modalities are often used in conjunction with medications. Options include simple analgesics, such as acetaminophen, propoxyphene or tramadol, or analgesics with anti-inflammatory properties such as the nonsteroidal anti-inflammatory drugs (NSAIDs). While acetaminophen may perform similarly to NSAIDs, patients often display strong preferences for certain classes of drugs. Interestingly, NSAIDs are prescribed more often for women than men with osteoarthritis, but the reason behind this

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gender difference is not clear.²⁰ Acetaminophen may be a safer option for most patients. COX-2-specific NSAIDs were initially believed to have a better safety profile than traditional NSAIDs, particularly with respect to serious gastrointestinal events, but their use has been reassessed due to a possible association with cardiovascular disease. Studies suggest that all NSAIDs, both traditional and COX-2-selective, may be associated with an increased risk for cardiovascular events, leading to changes in guidelines for their use.

A recent study of glucosamine and chondroitin sulfate showed an improvement in pain with glucosamine/chondroitin sulfate.²¹ This effect was limited to those patients with the most severe pain at baseline. The results of this study have been the subject of some criticism related to an unusually high placebo response rate, and the use of glucosamine hydrochloride rather than glucosamine sulfate. Accordingly,

the role of these supplements in treating osteoarthritis continues to be defined.

Topical agents, such as capsaicin-containing creams, can also be quite useful for some patients. Capsaicin is the active ingredient in hot chili peppers, and is believed to reduce pain by stimulating the release and ultimate depletion of substance P from sensory nerve endings. In one double blind, placebo-controlled study of osteoarthritis of the hand, 0.075% capsaicin applied four times daily significantly reduced pain and stiffness.²²

For amenable joints such as hips and knees, total joint replacement is an excellent option when less aggressive management strategies fail. Women tend to wait longer for joint replacements than men, citing concerns about risks of surgery and disruption of caregiver roles.²³ These surgeries typically decrease pain and significantly improve function for most patients. As joint prostheses and surgical techniques continue to improve, total joint replacement should be a viable option for an increasing number of patients with osteoarthritis.

Summary and Conclusions

In summary, osteoarthritis is a common condition with significant impact on the quality of life of affected individuals. Symptomatic osteoarthritis is more common in women than men, and its dramatic rise in incidence around the time of menopause remains an unexplained phenomenon. While a clear role for estrogen and other sex hormones remains elusive, delineating the factors contributing to osteo-

arthritis will, it is hoped, lead to more effective preventive measures and better therapies. ■

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From the Editor

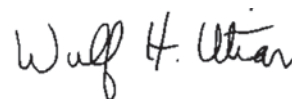
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health care. The responsibility to counsel women about risks and benefits of all pharmacotherapies is yours. You sign the prescription, you carry the liability. It is time to tell women, "Buyers beware!"

A bird's-eye view over 20 years truly makes me wonder whether life goes in circles. The immediate access to our comments and writings brought about by the new technology age should make all of us think twice before committing the thought to the document. I cer-

tainly do, and fortunately have little regret for what I have said thus far.

If you want copies of any of the complete editorials, please contact the NAMS office (info@menopause.org).



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