

## Low Estrogen Linked to Knee Osteoarthritis in Women

ANN ARBOR, Mich., July 26 -- Possible strategies aimed at boosting levels of estradiol and one of its metabolites are being considered to help prevent osteoarthritis of the knee in women approaching menopause, a study here suggested.

Women near menopause with the lowest levels of circulating estradiol were nearly twice as likely to develop osteoarthritis of the knee over a three-year period as women with higher levels of the hormone, reported MaryFran R. Sowers, Ph.D., and colleagues, of the University of Michigan.

Similarly, women with the lowest levels of 2-hydroxyesterone, an estrogen metabolite, were at nearly three times the risk, the researchers said in the August issue of *Arthritis & Rheumatism*.

"There has been an ongoing debate as to whether hormone levels contribute to the pathogenesis of osteoarthritis and/or serve as a biomarker of risk for the development of osteoarthritis," the researchers said.

However, most previous studies have focused on women undergoing hormone replacement therapy (HRT) for menopause, they said. Few studies have examined the relationship between natural endogenous hormone levels and osteoarthritis in women not on HRT, and none have looked at levels of estrogen metabolites, they noted.

The study included 842 premenopausal and perimenopausal women (average age: 42) from the Southeast Michigan Arthritis Cohort. For three years, these women underwent annual X-rays of both knees, and their blood levels of estradiol and urine levels of 2-hydroxyesterone and 16a-hydroxyesterone were measured.

After adjusting for age, injury, and body-mass index, women in the lowest tertile of estradiol level (less than 47 pg/ml) were significantly more likely to have developed osteoarthritis of the knee compared with women in the middle tertile (47 to 77 pg/ml; odds ratio=1.88; 95% confidence interval=1.1 to 3.5).

Similarly, women with the lowest levels of 2-hydroxyesterone were at increased risk for the disease (OR=2.9; 95% CI=1.5 to 5.7).

In addition, women with the highest ratio of 16a-hydroxyesterone to 2-hydroxyesterone were also at higher risk (OR=1.86; 95% CI=1.02 to 3.44).

Previous research has shown that estrogen metabolites play an important role in the metabolism of arachidonic acid, a compound necessary for synthesizing pro-inflammatory leukotrienes which, in turn, may contribute to the inflammation and pain of osteoarthritis, the investigators said.

Higher levels of estrogen metabolites such as 2-hydroxyesterone may inhibit the metabolism of arachidonic acid, thereby delaying the development of osteoarthritis, they speculated.

However, the relatively short study period "may not fully capture the arthritis development process," they said.

If, however, further study confirmed their speculations, "then considering alternative lifestyle and therapeutic pathways to influence these metabolites becomes increasingly viable," they concluded.

**Action Points**

Explain to patients who ask that this study documenting an association between low estrogen levels and knee arthritis suggests a possible pathway to development of osteoarthritis that may be targeted by therapies in the future, but no current prevention strategy is proposed.