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Sex hormones and the risk of osteoarthritis in women: epidemiological evidence

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Current concepts of the pathogenesis of osteoarthritis suggest a role for both systemic predisposition and site specific mechanical factors.[1] Sex hormones have long been considered a possible factor in the systemic predisposition to osteoarthritis, especially in women.[2-5] There are several lines of epidemiological evidence suggesting that sex hormones, primarily oestrogen, play a role in osteoarthritis. These include a female excess in the prevalence and incidence of osteoarthritis that begins around the time of the menopause, and the association of prevalent osteoarthritis with possible markers of endogenous sex hormone exposure, including gynaecological surgery (reviewed elsewhere in this supplement) bone mass, and obesity. In a provocative review, Spector and Campion[4] proposed that much of this evidence is consistent with the hypothesis that women with a greater exposure to endogenous oestrogen are predisposed to generalised osteoarthritis. On the other hand, studies that assess serum sex hormone levels in women with osteoarthritis are inconclusive. There is also a growing body of evidence to suggest that postmenopausal oestrogen replacement may protect against large joint osteoarthritis. It is possible that the effect of sex hormone exposure in osteoarthritis varies by menopausal status and stage in the extended pathogenesis of osteoarthritis.

Menopause

The prevalence of osteoarthritis in the hand, hip, and knee increases rapidly with age, beginning at about the age of 40-50 years in women, but less so in men, so that before the age of 50, men have a higher prevalence of disease than women, but after 50 women have a higher prevalence, and the incidence and sex differences increase with age.[6-10] Older women are also more likely to report joint symptoms for the same level of radiographic severity of knee osteoarthritis[11] and have more rapid progression of hip osteoarthritis than men.[12] Some investigators have suggested that women develop "menopausal arthritis" which consists of rapidly progressing osteoarthritis in the hand at the time of menopause.[2 3 13] Menopausal arthritis has been linked to generalised osteoarthritis with Heberden's nodes[3 13] which may be more common in women.[10] However, attempts to establish a temporal relationship between onset of generalised osteoarthritis and the menopause in individuals have been inconclusive.[3] Nevertheless, these patterns are broadly consistent with a role for postmenopausal hormone deficiency in increasing the risk or severity of osteoarthritis in women. In diseases such as heart disease, gout, and osteoporosis in which, like osteoarthritis, women's risk of disease rises dramatically after the menopause, oestrogen loss has been strongly implicated in disease risk.

Menopausal changes in systemic hormone levels are complex and include a profound longterm decline in oestradiol concentrations, lesser declines in oestrone and androgen concentrations, increased ratios of oestrone and testosterone to oestradiol, and decreases in sex hormone binding globulin, as well as increased short term fluctuations in cyclical levels of several hormones during the perimenopausal period.[14 15] Hot flushes, the most common menopausal symptom, are strongly associated with musculoskeletal pain[16] and appear to be linked to rapid fluctuations in serum oestradiol concentrations.[15] Spector and Campion[4] proposed that early perimenopausal declines in progesterone levels result in a temporary increase in levels of unopposed oestrogen which may predispose to osteoarthritis. Whether short term hormonal imbalances and fluctuations or permanent declines in hormone concentrations contribute to the surge in osteoarthritis risk which begins around the age of the menopause remains to be determined.

Bone density and obesity

The inverse relation of osteoarthritis with osteoporosis and the increased risk of osteoarthritis with obesity both suggest a possible role for oestrogen in osteoarthritis pathogenesis.[4] Oes-

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trogen regulates bone metabolism, and oestrogen deficiency causes bone loss in premenopausal and postmenopausal women[17]; a high bone mass in postmenopausal women is, in part, a marker for a greater lifetime exposure to oestrogen.[18] Postmenopausal women with knee, hip, hand, and multijoint osteoarthritis have an increased bone mineral density that is not explained by obesity.[19-22] This increased bone density is not due to slower postmenopausal bone loss in women with osteoarthritis[22] and may predate the menopause.[21] The association of osteoarthritis with high bone density may reflect increased biomechanical stress on cartilage in women with high bone mass[23] due to greater oestrogen exposure or could be due to a direct adverse effect of oestrogen on cartilage. On the other hand, high bone mass could be related primarily to osteophyte formation,[19 20] and the co-occurrence of these two features in "bone formers" may be explained by increased levels of bone or cartilage growth factor.[24]

Obesity is also associated with higher levels of endogenous oestrogen in postmenopausal women.[25] Obesity increases the risk of knee, hip, and hand osteoarthritis in women. (Felson DT, this issue, p 669) but whether this is due to the mechanical effect of weight on cartilage, higher estrogen levels or other systemic correlates of obesity is not known.[26]

Endogenous hormone concentrations

Two epidemiological studies have examined the relation of serum levels of sex hormones and osteoarthritis in postmenopausal women, with inconclusive results. Spector *et al*[27] studied early postmenopausal women with hand osteoarthritis defined by Heberden's nodes and found decreased levels of sex hormone binding globulin, possibly indicating higher levels of circulating free oestrogens and androgens, but no difference in oestradiol or testosterone concentrations. Cauley and colleagues[28] found no association of radiographic hand osteoarthritis with serum concentrations of oestrone, testosterone, or androstenedione in elderly Caucasian women. There are no published studies of serum sex hormone concentrations and knee or hip osteoarthritis.

Epidemiological studies of postmenopausal oestrogen replacement therapy (ORT) and osteoarthritis (OA)

Author/Year	*N*	*Design*	*Joint(s)*	*Definition of OA*	*Results**
Nevitt, *et al* 1994 (29)	4366	Cohort Cross-sect	Hip	*x* ray OA, Symptomatic OA	8.9% of current ORT users with OA *v* 12.9% non-users; adjusted OR = 0.7 (0.5,0.9).
Hannan *et al* 1990 (30)	831	Cohort Cross-sect	Knee	*x* ray OA	≥ 2 exams of ORT use, adjusted OR of *x* ray OA = 0.7 (0.4,1.2) compared with never users.
Wolfe *et al* 1994 (46)	1329	Case-control Cross-sect	Hip & knee	Symptomatic OA	Ever use of ORT associated with slight reduction of OA prevalence: adjusted OR = 0.9 (0.7,1.2). ORT users with milder *x* ray OA than non-users.
Samanta *et al* 1993 (47)	690	Case-control Cross-sect	Large joint (knee & hip)	Symptomatic OA	Ever use of ORT associated with decreased rate of large joint OA (crude OR = 0.3 Hand (0.1,1.4)) and decreased rate of hand OA (crude OR = 0.6 (0.2,1.9).
Zhang *et al* 1995 (31)	557	Cohort Longitudinal	Knee	*x* ray OA Incident/ progressive OA	4% of current ORT users with OA *v* 19% non-users; adjusted OR = 0.3 (0.01,1.2).

* OR, odds ratios adjusted for at least age and body mass index (or weight). All OR reported with 95% confidence intervals.
Cross-sect, cross sectional.

Exogenous sex hormones

Some of the most intriguing evidence linking female sex hormones with osteoarthritis comes from studies examining the risk of osteoarthritis in women on postmenopausal oestrogen replacement therapy (ORT). Several recent epidemiological studies have found that ORT is associated with a lower than expected risk of knee and hip osteoarthritis (table). Four studies have evaluated prevalent disease (two investigated primarily radiographic disease), and one examined incident and progressive radiographic disease. All have shown an inverse association between ORT use and the risk of osteoarthritis, although in one study the odds ratio was close to unity (0.9). A meta-analysis (unpublished data) of the four prevalence studies (using a combined endpoint of knee and hip osteoarthritis and a fixed effects approach) shows a pooled odds ratio of 0.76 (95% confidence interval 0.63 to 0.91). In the two largest prevalence studies, the inverse association was stronger when analysis was restricted to more severe or bilateral radiographic osteoarthritis,[29 30] and one study found a non-significant trend (odds ratio for current use = 0.6) for a lower risk of symptomatic moderate to severe disease.[29] More recently, Zhang *et al* reported that current ORT users in the Framingham study have an adjusted odds of 0.3 (95% confidence interval 0.1 to 1.2, P = 0.07) of incident or progressive radiographic knee osteoarthritis during eight years of follow up.[31] A stronger inverse association with disease among women receiving long term ORT was found for both prevalent radiographic osteoarthritis (10 years of use *v* one to nine)[29 30] and incident osteoarthritis (five years of use *v* one to five).[30] In contrast, another recent study found that current use of ORT was associated with a 40% non-significant increase, and long term ORT use with no difference, in the risk for a combined endpoint of incident clinical osteoarthritis of the knee, hip, or hand.[32]

Three studies[29-31] included adjustments for important confounding variables, including obesity, physical activity, smoking, reproductive history, and ovariectomy. Women with osteoporosis are more likely to be prescribed oestrogen, and osteoporosis may protect against osteoarthritis[23]; two studies adjusted for markers of osteoporosis.[29 31] Despite these attempts to adjust for confounding variables, women who use, and remain on, ORT differ in many ways from those who choose not to use

oestrogen[33] and this could explain the apparent protective effect of oestrogen.

Studies of the effect of oestrogen administration in animal models of osteoarthritis have been inconsistent. One study found that subcutaneous injections of oestradiol reduced the development of osteoarthritis lesions in a male mouse model.[34] Recently it was shown that ovariectomised sheep develop increased vulnerability of cartilage to shear and compression stress, but those treated with oestrogen do not develop such cartilage changes.[33] However, in meniscectomised female rabbits, Rosner and colleagues found that subcutaneous oestradiol administration increased, while that of the oestrogen agonist/antagonist tamoxifen decreased, erosive lesions in cartilage in both ovariectomised and non-ovariectomised animals.[5] Injection of oestradiol into the knees of ovariectomised rabbits has also been reported to produce osteoarthritis-like cartilage lesions, although the local irritating effect is unknown and the dose used was suprapharmacological.[35]

Mechanisms

Oestrogen could effect osteoarthritis through cytokines and growth factors which have a potential role in cartilage metabolism. For example, the cytokines interleukin (IL)-1 and tumour necrosis factor α (TNF-α), which can be produced by joint tissue, potentiate the production and activation of enzymes which degrade cartilage matrix.[36 37] Synthesis of IL-6 by articular chondrocytes may also play a role in cartilage metabolism, though this is uncertain.[37] The effect of oestrogen on bone metabolism appears to be mediated in part by these cytokines.[38 39] Oestrogen receptors are found in articular cartilage[40] and one study suggests that IL-1 and IL-6 may mediate an effect of oestrogen on cartilage metabolism.[41] The growth factors insulin-like growth factor 1 (IGF-1) and transforming growth factor β (TGF-β) may be involved in the synthesis and repair of cartilage matrix[42]; oestrogen has complex effects on the growth hormone-growth factor axis.[17 43-44]

Oestrogen may also influence the development of osteoarthritis through its effect on bone metabolism. Higher bone mass resulting from greater oestrogen exposure could cause increased mechanical stress on cartilage during joint loading.[23] Progressive cartilage degradation and rapid subchondral bone turnover are closely linked in osteoarthritis.[45] ORT reduces bone turnover in postmenopausal women[17] and could help stabilise osteoarthritis by slowing subchondral bone remodelling.

Other possible mechanisms by which oestrogen could influence the risk of osteoarthritis include protection against vascular defects in subchondral bone, greater neuromuscular protection against excessive joint loading, and through its antioxidant potential.

Conclusion

The evidence from epidemiological studies of the association of osteoarthritis with factors related to sex hormone exposure in women is conflicting and often difficult to interpret. There are many potential sources of bias and confounding in existing studies, which may not be adequately controlled for in the design or analysis. The hormonal correlates of the menopause and other potential markers of endogenous hormone exposure are complex, making implication of any specific hormonal changes in osteoarthritis risk uncertain. The natural history of osteoarthritis is not well enough understood, at present, to gauge the importance in older postmenopausal women of exposure to endogenous hormones 10 to 20 years previously. It is possible that oestrogen exposure has different effects depending on menopausal status or stages in the pathogenesis of osteoarthritis. High levels of oestrogen may act to increase the risk of disease in premenopausal women, either directly or through a higher bone mass, but slow the development or progression of disease in postmenopausal and elderly women. Increasing numbers of studies suggest that women on ORT have a lower than expected risk of radiographic osteoarthritis of the knee and hip. Clarifying the effect of postmenopausal hormone replacement therapy on osteoarthritis will probably require a randomised trial. Further epidemiological, clinical, and biochemical studies of the role of sex hormones in osteoarthritis among women is warranted.

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