Is there any rationale for prescribing hormone replacement therapy (HRT) to prevent or to treat osteoarthritis?

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Summary

Background: During the last two decades of the 20th century, hormone replacement therapy (HRT) has been considered as the sole pharmacological approach for counterbalancing or mitigating the effects of estrogens deprivation in post-menopausal women. Subsequently, HRT has been widely recommended for the management of chronic diseases occurring in women during the second half of their life.

The overall risk/benefit ratio of estrogens has been recently reassessed in the light of long-term prospective studies failing to demonstrate the expected benefit of HRT on cardiovascular diseases incidence. Osteoarthritis (OA) is one of the chronic conditions for which HRT has been suggested to provide beneficial outcomes.

Results: The presence of estrogen receptors in human cartilage is no longer debated. However, cellular or animal models of OA do not provide an unequivocal pathway for the influence of gonadal steroids on cartilage. Similarly, studies attempting to correlate serum or urinary levels of sex steroids to the onset or progression of OA gave conflicting results. No randomized, prospective, controlled trial was designed to specifically assess the impact of hormone replacement therapy on symptomatic or structural progression of OA. Large-scale observational studies or trials designed to assess other potential benefits of estrogens suggest that HRT use does not provide symptomatic relief in OA but may interfere with its long-term structural progression, particularly in the lower limbs.

Conclusion: Based on the recent results of the Women Health Initiative suggesting that HRT health risks may outweigh benefits, one can hardly recommend, with the current level of evidence, HRT as a first-line treatment against progression of OA. © 2003 OsteoArthritis Research Society International. Published by Elsevier Science Ltd. All rights reserved.

Key words: Osteoarthritis, Estrogens, Hormone replacement therapy, Treatment prevention.

Introduction

The prolongation of life expectancy has been one of the most impressive achievements of concerted Public Health strategies during the 20th century. However, this enormous medical progress has also generated new health-related challenges. The increase in life expectancy, combined with the drastic reduction in fertility rate observed in many developed countries, resulted in a marked increase in the population of elderly (over 65 years). These elderly subjects generated an immense demand on the social and health services to cope with their frailty, disability and dependence. The promotion of healthy aging and the prevention or reduction of morbidity in the elderly is now a predominant concern of Public Health policy makers. In most regions of the world, women continue to have significantly higher level of life expectancy than men. Since the mean age of menopause has remained remarkably stable over the last century, women now frequently face a period of several decades characterized by deprivation in sex hormones. Estrogens deficiency after the menopause has been linked to an increase of several chronic diseases including, but non-exhaustively, cardiovascular disorders, osteoporosis, Alzheimer’s disease and osteoarthritis (OA). During the second half of the 20th century, hormone replacement therapy (HRT) has been repeatedly promoted as the only pharmacological approach allowing a global prevention (or mitigation) of all disorders related to or potentiated by estrogen deprivation. Recently, the risk/benefit profile of HRT has been severely challenged because of apparent increased risks of invasive breast cancer, coronary heart disease events, stroke and pulmonary embolism among treated women. These new findings imply a careful reassessment of the current evidence justifying the prescription of HRT for the prevention or the management of chronic disorders. OA, the most common form of musculoskeletal disorder in aging women, has been linked to estrogen deficiency. OA is one of the disorders for which a detailed analysis of facts and assumptions supporting beneficial effects of HRT should be provided.

Assumptions from preclinical research

The presence of estrogen receptors (ERs) in cartilage from human and other species has been repeatedly...
reported. Some investigators found discrepancies in the presence of ERs relative to the sex of the donor or the type of cartilage studied.

A similar number of high affinity, low capacity binding sites of ERs were found in cultured chondrocytes derived from pre-pubertile or pubertile rabbits. The affinity of estrogen receptors for its ligand was higher in chondrocytes derived from pubertile rabbits compared with those obtained from pre-pubertile animals. In humans, cartilage cells from early neo-natal children did not respond to sex steroids (dihydrotestosterone and 17-β estradiol). The effect of sex steroids on human chondrocytes was reported to be maximum at the early phase of puberty and gonadal maturation. In cartilage from adult monkeys, treated with conjugated equine estrogens, RNA transcripts for both ER α and β were found and increased transcriptional activity in response to exogenous estrogens was noted in primary chondrocytes. Furthermore, in this investigation, a stimulation of insulin-like growth factor binding protein 2 (IGFBP2) production, most likely mediated by changes in insulin-like growth factor-1 (IGF-1) was reported, leading to higher levels of baseline sulfate incorporation in proteoglycans (PG) by chondrocytes from estrogen-treated animals. However, 17-β estradiol in the range of 10−12 M to 10−10 M did not stimulate chondrocytes, proliferation, collagen II and PG synthesis in a model of human chondrocytes in tridimensional culture.

In a surgically-induced rabbit model of OA, estrogen decreased PG synthesis but not the concentration of total PG. Supraphysiological concentrations of estrogen were also reported to reduce PG synthesis while physiologic concentrations had no effect on PG synthesis or chondrocytes proliferation. Eventually, in a limited series of human subjects from both genders, an increase in the estrogen receptors binding in cartilage from the medial compartment of the femoral condylar together with higher synovial estradiol levels were possibly linked to the development of knee OA. This observation was in accordance with previous findings from the same group, suggesting that up-regulation of ERs in the femoral condyle cartilage of rabbits was responsible for initiation of osteoarthritic changes in estradiol-treated animals. Injections of high (0.3 mg/kg body weight/day), but not low doses (0.06 mg/kg body weight/day), of estradiol were injected into knee joints of ovariecotomized rabbits, resulting in loss of condyle surface congruity, fissuring and fibrillation of the cartilage. After 3 months, cartilage erosion extended to the calcified layer, exposing the subchondral bone. All these features were antagonized when tamofoxene, a selective estrogen receptor modulator (SERM), was injected concurrently with estrogens. Conversely, estradiol implants in skeletally mature ewes prevented the deleterious effects of ovariecotmy on the intrinsic material properties (decrease in aggregate modulus and shear modulus) of the articular cartilage of the knee. From these pre-clinical results, it seems clear that close interactions exist between gonadal steroids circulating at local level and cartilage metabolism. The discrepant observations reporting either protective or deleterious effects of estradiol on chondrocytes, cartilage and surrounding tissues, are most probably related to the disparity in cellular or animal models tested. Through the presence of ERs in human cartilage, estradiol is most likely one of the factors to be considered in the expression of OA. However, at this stage, the real physiological role of gonadal steroids in the pathogenesis of OA remains quite equivocal.

Evidence from observational and clinical studies

OA presents a wide spectrum of clinical and structural manifestations. In 1925 Cecil and Archer described a form of polyarthitis of obese middle-aged women, occurring just after the menopause, associated with the presence of Heberden’s nodes, which was named ‘menopausal arthritis’. Since then, several investigations attempted to better define the influence of estrogen deficiency or replacement on OA occurrence and severity. The high incidence of generalized OA in perimenopausal women or in women just after the menopause raised two discrepant hypotheses. Some authors suggested that women with high endogenous estrogen concentrations are predisposed to OA, the effect being greatest around the menopause when the ratio of estrogen to progesterone is high. Others consider that estrogen deficiency at the menopause could play a significant role in causing disease.

Inconsistent results were found when assessing serum or urinary sex-hormone levels in women with OA. Generalized OA in women between 53 and 61 years was linked to a significant decrease in sex-hormone binding globulin (SHBG), suggesting that higher levels of free estrogens and androgens may have a role in the pathogenesis of this type of OA. However, no obvious difference for any of the hormones tested (testosterone, estradiol, SHBG and dihydroepiandrosterone) was seen in women aged over 61. Furthermore, while obese women have higher concentrations of endogenous estradiol, the authors did not unequivocally control for the degree of obesity in this population.

The obesity–OA relationship is less confounded by mechanical factors in hand OA. Therefore, this condition was seen as a more direct test of the hypothesis that endogenous estrogens are related to OA, independent of obesity. In a population of Caucasian women with a mean age of 74 years, similar concentrations of serum estrone, estradiol, testosterone and androstenedione, were found in mild, moderate or severe hand OA. Such data do not support an association between endogenous sex-steroid hormone concentrations and severity of hand OA in elderly women. Accordingly, no association between estrogen-related hormonal events (age at menarche or menopause, rates of hysterectomy, oral contraceptive use) was observed with the presence of either nodal generalized OA or non-nodal pauciarticular larger joints OA in a population of British women.

Menopause and the subsequent dramatic fall in circulating estrogens have been clearly identified as a major determinant of osteoporosis (OP). Another way to assess a possible impact of endogenous estrogens on OA is to investigate the relationship between OP and OA. Early studies suggested that these two conditions rarely coexist clinically, prompting the description of two distinct groups of patients, the lean osteoporotic and the fatter osteoarthritic. The presence of OA was linked with increased bone mass, muscle strength and fewer fractures. Indeed, surgeons noticed the general absence of osteoarthritic changes in femoral necks excised in the treatment of osteoporotic fractures of the femoral head. This observation was further supported by the description of a small increase in bone mineral density (BMD) in middle-aged women with early radiological OA of the hands, knees and lumbar spine, even after adjustment for age and body mass index (BMI). In patients from both genders, selected from the Baltimore Longitudinal Study of Aging, with osteophytes
described on standing knee radiographs, lumbar spine BMD (adjusted for age and BMI), but not hip BMD, was increased compared with matched controls. These results were slightly different from those of the Chingford Study and the Framingham Study, where higher adjusted mean BMD in the femoral neck was shown in women with definite knee OA. In the Framingham Study, however, adjusted mean femoral neck BMD was not increased in men with definite OA.

Most of these studies adjusted for confounding variables. However, discrepancies observed might be related to the matching for genetic factors. The inverse relationship seen between BMD and OA could be due to shared genetic factors between OA and high bone mass. This hypothesis was supported by the description, in the discordant twin model of an inverse relationship between OA and femoral neck BMD at the OA-affected hip only, but not at the contralateral hip, lumbar spine or total body. ER genotype, with the combination of the PvU II and Xba I RFLP has been reported to be a significant risk factor for severe generalized OA. These observations demonstrated that the inverse relationship between OP and OA is most probably dependent on other factors (e.g., anthropometric characteristics, increased growth factor synthesis, etc.) than endogenous estrogen levels. Whether occurrence or severity of OA is closely linked to endogenous sex-hormones production and whether high estrogen concentrations have a protective role on knee, hip, hand or spinal OA cannot be inferred from the currently published material.

The lack of understanding of the clear role of sex steroids in OA pathogenesis does not preclude a potential interest for HRT in prevention or treatment of OA in post-menopausal women. As is the case for HRT and OP, few if any proper studies were conducted, in accordance with the currently requested methodological standards, to demonstrate the effects of HRT in OA. Most of the evidence should thus be derived from either case-control studies or from observations made in the context of investigations designed to assess other potential properties of HRT.

The results of these investigations remain rather controversial. Most trials suggested a protective, often borderline significant, effect of HRT but others described either no benefit or an increased risk in HRT users.

In a population of German women aged 50 years and older who underwent hip or knee joint replacement because of advanced OA (the Ulm Osteoarthritis Study), the prevalence of OA in the contralateral joint or of generalized OA was similar among users and non-users of HRT. The relative hazards for bilateral or generalized OA in HRT users compared with non-users did not support the hypothesis that HRT is a systemic protective factor against OA.

As previously mentioned, the prevalence of hand OA is significantly higher in women than in men. There are few doubts that hormonal determinants, even if not yet fully understood, play a critical role in the onset of OA at this location. Therefore, hand OA could be an ideal target for the identification of a putative effect of HRT that could either potentiate the disease if estrogens play a deleterious role or reduce its severity if the pathophysiological process implies the menopause-related estrogen deficiency.

No significant protection (or deleterious effect) of HRT was observed in the Chingford Study, where current HRT users, ever users or past users, were compared with women who never received estrogens. Similar results resulted from a cohort of French women in whom HRT intake did not influence the symptomatic activity of hand OA.

At the hip, women from the Study of Osteoporotic Fractures who were currently using oral estrogens had a significantly reduced risk of any (OR: 0.62, 95% CI 0.49–0.86) and moderate to severe radiographic manifestations of OA (OR: 0.54, 95% CI 0.33–0.88). Current users who had taken HRT for 10 years or longer had a greater reduction in the risk of any OA (OR: 0.57, 95% CI 0.40–0.82) compared with that of users for less than 10 years (OR: 0.75, 95% CI 0.47–1.24). Current estrogen use for 10 years or longer was also associated with a non-significant trend for a reduced risk of moderate to severe symptomatic disease. There was a non-significant lower risk of OA of the hip among long-term users who stopped taking estrogens less than 10 years prior to their examination. No reduction was observed in risk among the subjects who stopped taking estrogens 10 or more years previously. These results support that HRT, prescribed for several years and never stopped, may protect against the development or progression of radiographic findings of OA of the hip. From this analysis, however, the effects of HRT on symptoms of hip OA remain much more questionable. No group (even current users for more than 10 years) experienced a significant reduction in the risk of presenting a symptomatic moderate to severe hip OA. A case-controlled study compared women listed for hip replacement because of primary OA with women selected from the general population. In these studies, short-term HRT use (up to 5 years duration) was associated with a borderline significant excess risk of hip OA (OR: 1.7, 95% CI 0.9–3.3) while more than 5 years of use were associated with a 40% non-significant reduction in risk. The authors related the surprising increase in relative hazards with short-term HRT to the possible preferential prescription of HRT to women who were more symptomatic and who were seeking for more medical care.

The Heart and Estrogen/Progestin Replacement Study (HERS), a study initially designed for the assessment of HRT in prevention of coronary heart diseases in post-menopausal women, failed to demonstrate any effect of 4 years of HRT compared to placebo in the percentage of women reporting knee pain, the severity of pain or related disability. However, when measuring articular knee cartilage, by magnetic resonance imaging, in long-term HRT users (more than 5 years) users Wuika and colleagues noted a significant increase in tibial cartilage volume (+7.7%) in the group of HRT users that persisted after the exclusion of women with OA. A protective effect of HRT for knee OA, defined by osteophytes (OR: 0.31, 95% CI 0.11–0.93), and a similar but not significant effect for moderate joint space narrowing of the knee was reported for current HRT users at baseline of the Chingford study. For ex-users, there was no protective effect of HRT for knee OA. However, on X-rays taken after 4 years follow-up, current HRT was only associated with a non-significant protective effect for incident knee osteophytes. These results were supported by those issued from the Framingham Study where a modest but non-significant protection effect for both radiographic OA and severe radiographic OA was seen in women who reported estrogen use at two or more examinations. After 8 years of follow-up, current estrogen users had a 50% non-significant reduction in the risk of incident radiographic knee OA compared with never users and a trend towards decreased risk of progression of knee OA compared with women who never used HRT. An increase in the risk of developing severe knee OA, leading to prosthetic surgery,
was described in women receiving HRT in the Swedish Knee Arthroplasty Register (RR 1.8, 95% CI 1.2–2.6) but this study did not mention HRT duration or the reason for HRT prescription.  

Conclusion

In conclusion, the relationship between estrogentic status of peri- or post-menopausal women and the occurrence of OA has been suspected for many years. Estrogens and, more generally, gonadal steroids have been presented as protective factors by some authors and as pathogenic determinants of OA by others. In vitro and animal studies, notwithstanding the unequivocal description of ERs in the articular cartilage, do not provide a satisfactory and widely accepted mode of action of estrogens on the chondrocytes and surrounding tissues. Studies that attempted to link circulating levels of gonadal steroids in women with the prevalence or severity of OA yielded conflicting results. This can most likely be attributed to the heterogeneity of OA and the long duration between the initiation of the OA process and the time of the assessments. More interesting are the studies that assessed the impact of ERT or HRT on the progression of OA in post-menopausal women. While the symptomatic action of HRT in OA appears to be marginal, several large observational studies concluded that long-term HRT may have a beneficial effect on the structural progression of OA, particularly at the lower limbs (knee and hip). Unfortunately, as for post-menopausal osteoporosis, no randomized controlled study aiming specifically at the assessment of the effects of HRT on structural progression of OA is currently available. This lack of evidence-based information and the observation that only long-term HRT appears to be beneficial should be carefully considered when assessing the interest of HRT for the management of OA. This global risk/benefit ratio becomes even more hypothetical, in the light of the most recent publications questioning the other putative long-term benefits of HRT.

References


