The influence of sex hormones on musculoskeletal pain and osteoarthritis

Malvika Gulati MRCP, Eren Dursun MSc, Katy Vincent DPhil, Fiona E Watt FRCP

Full name, postal address and e-mail of corresponding author:
Dr Fiona Elizabeth Watt, FRCP
f.watt@imperial.ac.uk
Centre for Inflammatory Disease, 9th Floor, Commonwealth Building, Department of Immunology and Inflammation, Hammersmith Campus, Imperial College London, London, Du Cane Road, London, W12 0NN. United Kingdom

- *Centre for Osteoarthritis Pathogenesis Versus Arthritis, Kennedy Institute of Rheumatology, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS), University of Oxford, Oxford, United Kingdom*
- *Rheumatology Department, Charing Cross Hospital, Imperial College Healthcare NHS Trust, London, United Kingdom*
- *Rheumatology Department, Nuffield Orthopaedic Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom*

Full name, department, institution, city and country of all co-authors:
Malvika Gulati, MRCP

- *Centre for Osteoarthritis Pathogenesis Versus Arthritis, Kennedy Institute of Rheumatology, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS), University of Oxford, Oxford, United Kingdom*

Eren Dursun, MSc

- *Centre for Inflammatory Disease, 9th Floor, Commonwealth Building, Department of Immunology and Inflammation, Hammersmith Campus, Imperial College London, London, Du Cane Road, London, W12 0NN. United Kingdom*

Katy Vincent, DPhil

- *Nuffield Department of Women's and Reproductive Health, University of Oxford, Oxford, United Kingdom*

Fiona E Watt, FRCP

- *Department of Immunology and Inflammation, Imperial College London, London, United Kingdom*

- *Centre for Osteoarthritis Pathogenesis Versus Arthritis, Kennedy Institute of Rheumatology, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS), University of Oxford, Oxford, United Kingdom*
- *Rheumatology Department, Charing Cross Hospital, Imperial College Healthcare NHS Trust, London, United Kingdom*

Keywords: osteoarthritis; musculoskeletal; sex; pain; hormone; 'HRT'; estrogen; menopause

Running header: Sex hormones, pain & OA

SUMMARY

The association of female sex with certain rheumatic symptoms and diseases is now indisputable. Some of the most striking examples of this association occur in individuals with musculoskeletal pain and osteoarthritis, in whom sex-dependent changes in incidence and prevalence of disease are seen throughout the life-course. Joint and muscle pain are some of the most common symptoms of menopause, and there is increasingly compelling evidence that changes in or loss (be it natural, autoimmune, pharmacological, or surgical) of sex hormones influences musculoskeletal pain propensity and perhaps disease. However, the effects of modulation or replacement of sex hormones in this context are far less established, particularly whether these approaches could represent a preventative or therapeutic opportunity once symptoms have developed. In this Review, we present the evidence for the association of changes in sex hormones with musculoskeletal pain and painful osteoarthritis, discussing data from diverse natural, therapeutic, and experimental settings in humans and relevant animal models relating to hormone loss or replacement and the consequent effects on health, pain, and disease. We also postulate mechanisms by which sex hormones could mediate these effects. It is clear that much more research is needed, but increased scientific understanding of this complex area may lead to real benefits in musculoskeletal and women's health.

Introduction

Roughly one-third of people (>20 million in the UK alone) live with a musculoskeletal condition, many of which are associated with pain (1, 2). The prevalence of common painful musculoskeletal conditions—including low back pain, neck pain, and osteoarthritis—is increasing, collectively accounting for around a fifth of years lived with disability worldwide (3). Osteoarthritis is the most common form of arthritis, affecting over 500 million people worldwide and is one example of a burgeoning spectrum of conditions that cause pain, suffering and work disability, which are strongly associated with the presence of comorbidities (4). One of the striking things about most of these conditions, besides their high prevalence and impact, is their association with female sex. Clinicians specialising in musculoskeletal conditions might take for granted that they see a preponderance of females in mid-life and later life presenting with these conditions, but what is it about the life-course that drives this predisposition? Understanding the underlying drivers of this observation could provide insight into mechanisms of musculoskeletal pain, illness, and disease, could help to define clinically relevant subgroups at high risk of disease, and might reveal new therapeutic opportunities. In this Review, we explore the evidence for an association between sex hormones (or their change over time), musculoskeletal pain and osteoarthritis and discuss the potential underlying mechanisms at play.

Sex and Musculoskeletal pain

Substantially more women live with chronic pain (from any cause), chronic widespread pain, and osteoarthritis (including hand, knee, and hip) (5-7). Individuals with these conditions probably represent the tip of an iceberg with regard to musculoskeletal pain, as many individuals without a formal musculoskeletal diagnosis also experience intermittent or chronic joint or muscle pain. Notably, the prevalence of painful, non-musculoskeletal conditions, including migraine, tension headache, irritable bowel syndrome, pelvic pain, and interstitial cystitis is also higher in females than males throughout most of the life-course. Although data are relatively limited, no sex difference among children with chronic pain is apparent; however rates of chronic pain in girls increase after puberty and are dependent on pubertal age, not chronological age (8). Younger age at menarche appears to modestly increase the risk of hip or knee replacement, as does increased parity (9). Interestingly, young (ie, pre-menopausal) female mice are relatively protected from osteoarthritis compared with male counterparts, meaning that most osteoarthritis studies in mice use exclusively male animals (10).

Sex steroid hormones (estrogens, progestogens, and androgens; herein referred to as sex hormones) are regulated centrally by gonadotrophin-releasing hormone, which is produced by the hypothalamus, and the pituitary gonadotrophins (follicle-stimulating hormone and luteinising hormone), with enzymatic control of the synthesis and bioavailability of these

hormones differing at various sites in the body (table 1; figure 1)(11). The effects of sex steroids are mediated through genomic and non-genomic pathways, involving classic membrane-bound receptors that bind to hormones at the cell surface and intracellular receptors that regulate transcription (11, 12). Levels of sex hormones change over the life-course (figure 2). They have roles far beyond sex and reproduction, including effects on the immune, metabolic, musculoskeletal, and central and peripheral nervous systems (11, 13, 14). Of relevance to this Review, connective tissue cells including osteoclasts, osteoblasts, and articular cartilage chondrocytes express both aromatase and sex steroid receptors and respond to sex hormones (15, 16). Levels in specific areas of the body are influenced by local synthesis by aromatase, for instance in articular cartilage, adipose tissue and brain (17-19).

Menopause, musculoskeletal pain, and osteoarthritis

The incidence of musculoskeletal conditions, most of which cause pain, is particularly high in older women, raising the possibility that these conditions are influenced by life-course factors including changes in sex hormones. A large number of epidemiological studies examining the effects of menopause and perimenopause on musculoskeletal pain and osteoarthritis have been done and are reviewed elsewhere (13, 20-24). Cohorts are often studied because menopause data are not typically collected in routine healthcare settings. These studies have shown associations between menopause and increased occurrence of joint pain and osteoarthritis (including joint replacement surgeries) (25). For example, joint pain and stiffness were common (53.6% of the population at baseline) among 438 women followed for 9 years. These symptoms were significantly more likely to occur in post-menopausal women than in their pre-menopausal counterparts (OR 2.28 [95% CI 1.34-3.87]), whereas no association was seen with chronological age (26). In another large study of over 40,000 women, osteoarthritis was more common among those who had experienced natural menopause (9210/29,793 [31%]) or surgical menopause (1417/4571 [31%]) at least one year earlier, compared with those whose menstrual period was within the last year (1915/8071 [24%]) (27). Low back pain, one of the most common painful conditions, also increases around menopause (28). Later age at menopause and longer reproductive span have both been shown to protect against total knee replacement, a surrogate for knee osteoarthritis (29). Among more than a million women included in this study from Korea, women whose age at menopause was 50-54 years were at lower risk of total knee replacement compared with those experiencing menopause age 40 years or less (adjusted hazard ratio [aHR]0.89 [95% CI0.84-0.94]); women with a 35-39 year reproductive span were also protected vs a reproductive span of less than 30 years (aHR 0.87 [0.85-0.89]) (29).

However, there are confounders that make interpretation of these studies challenging. Age must be accounted for in any study that tests associations with menopause. Also, musculoskeletal pain (arthralgia, myalgia) is one of the most common features of the

menopause syndrome worldwide, affecting up to 40-60% of women (25, 26, 30, 31), and it is the predominant symptom for about 20% of women (even higher in some ethnic populations) (31). As such, disentangling transient menopause-related joint or muscle pain from early osteoarthritis or a chronic pain syndrome of other aetiology is challenging. Understanding these differences often requires longitudinal follow up, whereas many published studies are cross-sectional in design.

Effects of exogenous sex hormone therapy

Hormone replacement therapy (HRT), also known as menopause hormone therapy, is effective in managing symptoms of menopause when there are no contraindications to its use (32). Examining use of HRT or other hormonal agents in human studies provides insights into the role of sex hormones in musculoskeletal disorders and pain, as these agents contain exogenous estrogen, often along with a progestogen or selective estrogen receptor modulator (SERM) to ensure uterine protection.

In two recent reports, prior use of HRT was associated with increased risk of total knee joint arthroplasty (29, 33). In the large Korean population study (29), women taking HRT for more than five years had an increased risk of undergoing both knee (aHR 1.23 [95% CI 1.17-1.29]) and hip (aHR 1.46, [1.12-1.89]) replacement surgery. However, this effect is likely to be bidirectional. In the general population, it is likely that menopause-related symptoms (including musculoskeletal ones) are present and documented in HRT users due to the fact that this drug class is licensed and prescribed for menopausal symptoms. (32)T, and those seeking HRT for their menopause syndrome may do so in part for musculoskeletal symptoms.

These factors may partly explain why there are a number of conflicting epidemiological studies regarding the effects of HRT on the prevalence or incidence of painful musculoskeletal conditions (34, 35). In a case control study of patients with hand osteoarthritis, overall HRT use had no effect on the incidence of hand osteoarthritis, although the odds of developing disease decreased among women in whom HRT therapy was initiated within 3 months of menopause (adjusted OR 0.72 [0.55–0.96])(36). Another reason for discrepant data is that some studies examine structural joint changes rather than symptoms. In the UK Chingford longitudinal cohort study of 985 women with x-rays of hands and knees, 143 (14.5%) had osteophytes suggestive of knee osteoarthritis and 140 (14.2%) had hand osteoarthritis based on distal interphalangeal joints. Current (but not prior) use of HRT had a protective effect on the development of knee osteoarthritis as defined by osteophytes (OR 0.3 [0.11-0.93], adjusted for age, height, weight, menopausal age, and bone mineral density), with a similar but non-significant effect for distal interphalangeal joint osteoarthritis (OR 0.48 [0.17-1.42]) (37). Ultimately, randomised controlled trial (RCT) level evidence may be necessary to unpick the true effects of HRT, at least on prevalent painful musculoskeletal conditions.

Large RCTs of women taking HRT for indications of classical menopause symptoms such as vasomotor symptoms, urogynaecological symptoms, or post-menopausal osteoporosis offer high quality, rich source of data for the effects of sex hormones in humans (table 2). Although no large trials (>200 participants) included women specifically on the basis of symptoms of musculoskeletal pain or osteoarthritis, many trial participants would be expected to have musculoskeletal pain, and some studies included secondary musculoskeletal outcomes. In a placebo-controlled RCT of HRT efficacy on menopausal symptoms in 16,608 women from the Women's Health Initiative, joint pain or stiffness was common prior to HRT (20%-24.9%, increasing with higher age), and individuals receiving HRT showed greater improvement of these symptoms compared with those who received placebo, although differences were modest (OR 1.43 [1.24-1.64]; table 2) (38). HRT treatment was also noted to significantly reduce the incidence of new musculoskeletal symptoms; for example, new general aches and pains were seen in 11% of those on active drug compared with 14.4% on placebo (OR 0.73 [0.66-0.82]). In post-hoc analyses of this trial, these modest effects were noted to occur primarily in women who had undergone hysterectomy using conjugated estrogens only (39). In a smaller RCT, women taking HRT were also less likely to report symptoms of aching joints and muscles than women on placebo (57% v 63%; p=0.001) (40). In the Women's Health Initiative trial, a lower frequency of knee and hip arthroplasty was seen in women taking estrogen only, but not in those on combined therapy of estrogen plus progesterone compared with placebo (41); this effect was corroborated for hip arthroplasty in a subsequent meta-analysis (42).

Until recently, no trials of HRT had been done in women with osteoarthritis or other painful musculoskeletal conditions. The lack of RCTs in this setting may be due in part to the relatively more recent discovery of estrogen receptors in joint tissues other than bone, and perhaps also to the highly publicised early closure of the Women's Health Initiative and subsequent worldwide reduction in HRT prescribing. At the same time, during the 2000s, one of the primary musculoskeletal indications for HRT—post-menopausal osteoporosis—became largely obsolete because of cheaper, safer, more effective drugs (eg, bisphosphonates) that prevented osteoporotic fracture. Nonetheless, the lack of RCT data for a primary musculoskeletal pain indication is still surprising given the available evidence of a possible protective effect of HRT. The acceptability of HRT for this indication and the feasibility of recruiting a sufficient trial participants of a single sex (for any condition) need to be considered. Our group therefore carried out a feasibility RCT of HRT in postmenopausal women with painful hand osteoarthritis (HOPE-e study) that included primary feasibility outcomes such as recruitment and retention rates to document how willing people might be to participate in such an RCT and how many had medical exclusions (43). The study also collected secondary outcomes focussed on measures of hand pain and function relevant to osteoarthritis. Although the study was not powered to detect efficacy, it met its prespecified feasibility criteria for progression to a full trial (recruitment of at least

22 participants in 12-15 months and dropout rate less of 30% or less), with a suggestion that HRT might have reduced overall menopausal symptoms. Another small RCT showed that treatment with the non-steroidal selective estrogen receptor modulator raloxifene (licensed for post-menopausal osteoporosis) combined with the vitamin D analogue alfacalcidol relieved knee pain symptoms in people with painful knees, back pain or both compared with alfacalcidol alone (44)(table 2).

The data from the raloxifene study are of interest given strong preclinical evidence that selective estrogen receptor modulators have beneficial effects on cartilage and bone (45). Prospective data suggest that musculoskeletal pain in individuals with osteoporosis improves in response to raloxifene (46). In a recent RCT, a form of HRT (combined with a form of exercise therapy) was tested in a group of post-menopausal women with painful greater trochanteric bursitis, using a 2x2 factorial design (47). Those with a BMI lower than 25 were found to have additional benefit of HRT plus exercise compared with placebo plus exercise.

In men, one RCT tested exogenous testosterone in chronic pain syndrome and late onset hypogonadism and found a significant improvement in bodily pain scores with testosterone compared with placebo (48). Another trial of testosterone supplementation in men with opioid-induced androgen deficiency showed improvement in hyperalgesia when compared with placebo, but no difference in self-reported pain scores (49).

These studies jointly point to a possible beneficial effect of sex hormone replacement in hormone-deficient individuals with musculoskeletal pain and potentially on other osteoarthritis outcomes, but no fully powered trials in target populations have been done.

The transgender population represent a unique group in which it is potentially possible to study the effects of sex hormone therapy on incident and prevalent painful conditions at the time of gender transition. Male-to-female individuals are given estrogen and anti-androgens whereas female-to-male are given androgens (50). Studies which examine musculoskeletal associations with gender-affirming hormone therapy suggest that although any individual undergoing this can experience musculoskeletal pain, female-to-male individuals have high frequencies of pre-existing pain (50, 51). Treatment with estrogen and anti-androgens may have a tendency to increase incident headache and musculoskeletal pain, whereas testosterone reportedly decreases pain symptoms (50). However, no definite associations can be established in what are a few small case series, and larger studies are needed. Pain outcomes in these studies might also be confounded by conditions that are known to be more common in these populations, such as sleep disorders, anxiety or depression (51).

Effects of sex hormone deprivation

Various surgical, autoimmune, and pharmacological scenarios give rise to acute deprivation of estrogen and other sex hormones, settings that may give further insight into the influence of sex hormones on pain. One such scenario is surgical bilateral ovariectomy (oophorectomy). This procedure reduces not only circulating estrogens, but also circulating androgens produced by the ovarian stroma (12). In one study, 162 women with a history of hysterectomy (which would be associated with ovariectomy for many, though this was not examined) had higher frequencies of radiographic knee osteoarthritis and first carpometacarpal joint osteoarthritis (32 [20%] vs. 16 [10%]), and higher relative rates for knee osteoarthritis (4.89 (95%CI 2.21-10.80]) and first carpometacarpal joint osteoarthritis (2.28 [1.12-4.29]) than 164 age matched controls without hysterectomy. This excess risk was similar following adjustment for age, obesity, parity, and smoking status (52). In a cross-sectional study of women (mean age 53 years) attending menopause clinics, there was increased risk for developing osteoarthritis in those with surgically-induced menopause (OR 1.13 [1.07-1.21] and after spontaneous menopause (1.18 [1.08-1.28])(27). Another example of ovarian functional loss, premature ovarian insufficiency (caused by mutations in the gene encoding the Fanconi anaemia group L protein [*FANCL*]) has been linked to increased risk of osteoarthritis in a genome-wide association study meta-analysis of 826,690 individuals, though definitive evidence is absent (53, 54).

Pharmacologic treatment can also result in deprivation of sex hormones, including drugs that cause intentional pharmacological sex hormone depletion used in the treatment of hormone-sensitive cancers (55, 56). For example, a key therapeutic approach to hormone receptor-positive (HR+) breast cancer is the use of aromatase inhibitors (55). Aromatase inhibitors competitively bind the aromatase enzyme, thereby inhibiting the conversion of androgens into estrogens and depleting the (already low) estrogen levels in post-menopausal women with HR+ breast cancer. While these drugs improve prognosis in HR+ breast cancer, common adverse events associated with their use include hot flushes and musculoskeletal symptoms such as arthralgias, myalgias, joint stiffness, and carpal tunnel syndrome (collectively known as aromatase inhibitor-induced musculoskeletal syndrome, or AIMSS)(57). In a study of 503 women with early-stage breast cancer initiating an aromatase inhibitor, 24% of patients discontinued therapy due to musculoskeletal symptoms (58). Risk factors associated with AIMSS included high/low BMI, prior taxane-based chemotherapy, co-existing arthritis or osteoporosis. In an analysis of data from ATAC trial of the aromatase inhibitor anastrozole or tamoxifen in women with breast cancer, 777 (41%) of 1914 women who had previously used HRT developed joint symptoms compared with 1001 (28%) of 3519 women without previous HRT use (OR 1·72 [1·53–1·93]) (59). Interestingly, in the same study, women with HR+ breast cancer developed significantly more joint symptoms in response to treatment than did those with HR-negative tumours (1556/4548 [34·2%] vs 124/461 [26·9%]). Diagnostic criteria for two groups within AIMSS have been suggested (table 3) (60).

Very few studies have documented osteoarthritis in the setting of aromatase inhibition by systematically examining joints and applying clinical diagnostic criteria. A case series of 77 post-menopausal women receiving outpatient treatment for non-metastatic estrogen receptor-positive breast cancer found that a higher proportion of patients with arthralgias in response to aromatase inhibitor treatment developed clinical hand osteoarthritis compared with those without arthralgias (28% vs 14%); however, this was not statistically significant (61). 14/25 (56%) participants with AIMSS had flexor tenosynovitis on ultrasound in one study compared with 7/23 (30%) without AIMSS (62). A direct effect of estrogen deprivation on connective tissues has been postulated as the likely mechanism for AIMSS (57). Alternatively, it is possible that increased pro-inflammatory cytokine release (documented in those with lower estrogen) could have effects on connective tissues or neurons (63).

Studying women stopping HRT as a form of estrogen withdrawal is also of interest. Reduction in hormone levels in this context is likely to be more abrupt compared with physiological estrogen decline associated with natural menopause, particularly when withdrawal is undertaken for reasons of safety or tolerability. Among women who were participants in the Women's Health Initiative who stopped combined HRT, the prevalence of joint pain or stiffness (26.4%) was double that of women who stopped taking placebo (14.4%); the rate of general aches and pains were also higher (22% vs. 11.5%) (64). In a nested case control study of 438,674 women included in an inception cohort at aged 45 years, women who stopped taking HRT within 18 months of inclusion in the study had increased odds of developing incident hand osteoarthritis compared with those with no prior HRT use (adjusted OR 1.25 [95% CI 0.86-1.81]). This risk decreased (eventually to null) with increasing duration between HRT cessation and study index date (36).

In the HOPE-e RCT, outcomes were assessed after the end of the study, following a phased tapering of study medication over four weeks (43). Immediately following HRT withdrawal, hand pain worsened in 46% of participants in the active treatment arm, but in only 17% of individuals on placebo, with the increase in average hand pain symptoms appearing to fall within a clinically significant range (though the study was not powered to detect this clinical effect and more data are needed).

Considering all of this evidence together, it is possible that the relative change in hormone levels and speed of this are more important than absolute concentrations, and that stabilisation of hormone levels, or else their gradual change where possible, is likely to be critical for protection from musculoskeletal pain. (There is currently no clear guidance on the tapering of HRT when stopping for non-safety reasons). Following this premise, the oral contraceptive pill or agonists of gonadotrophin-releasing hormone, which abolish hormonal fluctuations, have both been used therapeutically to improve pain in conditions such as inflammatory bowel syndrome endometriosis and chronic pelvic pain (65).

Rodent models of osteoarthritis and musculoskeletal pain present an opportunity to further investigate the relationships between sex hormone deprivation and musculoskeletal pain or osteoarthritis from a mechanistic standpoint (66). These studies primarily relate to the knee joint (there is no animal model of hand osteoarthritis), mostly using surgically-induced models of post-traumatic osteoarthritis. After medial meniscus destabilisation, osteoarthritis severity is markedly higher in male mice than females (66). However, surgical ovariectomy resulted in loss of protection from knee osteoarthritis in females, with rates becoming equivalent to orchidectomised males (10). This loss of protection was reversed by administration of 17b-estradiol. Further studies in rats provided evidence that exogenous estrogen counters the acceleration of type 2 collagen degradation and related structural alterations induced by surgical ovariectomy (67). This study also emphasised the importance of the timing of estrogen initiation relative to ovariectomy: delayed initiation resulted in lower protection against cartilage lesions. However, there have been apparently contradictory findings on the effects of ovariectomy in female mice. In a more recent study, ovariectomised females did not have different disease scores following partial meniscectomy compared with their non-ovariectomised counterparts (68). It is not clear whether this was due to the earlier timing of the ovariectomy, thereby allowing for adaptation. Pain thresholds in female rodents are also reduced by ovariectomy, and estrogen replacement in this context normalises these thresholds (69, 70). A reduction in pain threshold was shown after treatment with the aromatase inhibitor letrozole in ovariectomised female rats (63). In addition, orchidectomised male mice displayed greater pain-related behaviour following noxious stimuli than intact males, an effect likely mediated by testosterone (71, 72).

Overall, rodent models tend to support a critical role for sex hormones in the sex-dependent modulation of the pathogenesis of musculoskeletal pain and osteoarthritis. However, the substantial differences in the reproductive life-courses make direct inferences between mouse and man challenging.

Relevant molecular predictors of pain and osteoarthritis

Endogenous concentrations of sex hormones constitute potential molecular predictors of musculoskeletal pain and osteoarthritis, although there are numerous considerations (and pitfalls) around measuring sex hormones. These include species, diurnal variation, timing within the menstrual cycle (for menstruating women), hormonal fluctuations around the menopause and its effects on hormone binding proteins. With these points in mind, several studies have quantified sex hormones (or their precursors) and tested their association with musculoskeletal pain. In a small study of patients with fibromyalgia (17 patients and 19 healthy controls), concentrations of dehydroepiandrosterone sulfate (DHEA-S)—an endogenous steroid hormone precursor—correlated with pain threshold and pain tolerance (73). A similar association was reported in a study of 189 adults, with musculoskeletal pain

correlating with DHEA-S levels in a multivariate model that included important confounders such as age, sex, and BMI (74). A recent report of 9811 community dwelling adults (mean age 65 years) showed an association between lower sex hormone levels and chronic pain after adjusting for age and BMI (75). Interestingly, women with androstenedione or estradiol levels in the lowest tertiles had increased chronic pain compared with those with higher levels (ORs 1.20 [95% CI 1.03-1.39] and 1.27 [1.10-1.48] respectively). Estradiol levels were lower in men with chronic pain, but not women. In the same study, a cohort of more than 3000 people without pain at baseline was followed longitudinally, showing that low 17-hydroxyprogesterone concentrations in women was associated with a 38% increase in incident pain (75). Greater circulating levels of estradiol and androstenedione were also associated with protection from knee replacement and hip replacement for osteoarthritis, respectively, in 2600 women in an Australian cohort study (76). Lower levels of testosterone were associated with pain and hand osteoarthritis in a study of 573 women aged 24-45 years (77), but a study of men (aged 40-79 years) showed no such association (although associations between pain and higher concentrations of lutenising hormone and follicle stimulating hormone were seen) (78).

In the past 10 years, large human cohort studies have focused on the identification of metabolic and genetic associations of chronic pain or osteoarthritis in a hypothesis-free manner. In a study in 2444 adult female twins (mean age 58 [SD 10.6] years) from the UK Twins registry, investigators used metabolomic screening and found that low levels of epiandrosterone sulfate, a derivative of DHEA-S, were strongly associated with chronic widespread pain, even after adjusting for relevant covariates including fat mass (79). A single nucleotide polymorphism (SNP) was found to be closely associated with epiandrosterone sulfate concentrations. Interestingly, mendelian randomisation analysis suggested that levels of epiandrosterone sulfate were unlikely to be causally associated with chronic widespread pain. Rather, they suggested that steroid hormone changes resulted from the pain, although residual confounding could not be excluded (79). In a separate study, low levels of plasma androstenedione, another derivative of DHEA-S, were associated with an increased risk of lower limb arthroplasty due to osteoarthritis in men, particularly in those with obesity (80).

These studies collectively support a predictive association of sex hormone measurements with musculoskeletal pain and possibly osteoarthritis in both males and females which is both dynamic and complex.

In another large international consortium, a GWAS meta-analysis of osteoarthritis cases (any site) versus controls was done, including a female-specific sub-analysis of 90,000 cases and 192,000 disease-free controls (53). This study identified three sex-specific SNPs in women, two in hip osteoarthritis (nearest genes *FANCL*, *C8orf34*) and one in any site osteoarthritis (*UBAP2*). *FANCL* mutations are of note as they can be causative for premature ovarian

insufficiency in humans, as discussed above (54). The *C8orf34* SNP has previously been associated with waist-to-hip ratio, with opposite effects in men and women. *UBAP2* has been associated with type 2 diabetes, BMI, and bone mineral density. Though not sex-specific, *CYP19A*, which encodes for aromatase was also identified (53). However, reports of associations of human osteoarthritis with estrogen receptor gene polymorphisms were not reproduced in this larger metanalysis (81).

Mechanisms underlying sex hormone effects

Sex hormones may mediate their effect on musculoskeletal pain and symptomatic osteoarthritis in a number of ways. These include direct effects on pain sensing and perception, indirect effects on inflammatory or immune pathways, and direct effects on connective tissues (22, 23) (figure 3).

In a mouse model of knee osteoarthritis, females had similar levels of pain behavior than did males, despite lower chondropathy scores (68). Females also had greater upregulation of pain-associated genes in cartilage, without differences in cartilage repair. The authors speculated that in the mouse, pain at an earlier stage of chondropathy may protect females from progression. This could be via the female animals avoiding excessive loading of the abnormal joint at an earlier stage.

Sex hormones can modify pain experience by modulating neural pathways, both peripherally and in the central nervous system, and they might do so differentially in males and females (82, 83) (figure 3). Estrogen is a key modulator of pain behaviour, but its effect depends on concentration; in females, estradiol is anti-nociceptive at higher concentrations (activating inhibitory pathways in the spinal cord) and pro-nociceptive at lower concentrations in both mice and men (84, 85). In women who experienced trauma, lower levels of estradiol were associated with increased vulnerability to chronic pain (86). Progestogens are also antinociceptive, associated with pregnancy-induced analgesia in humans (87). Testosterone is a factor in protecting male mice from widespread pain compared with females and is also anti-nociceptive in humans (72, 85).

The influence of sex hormones on pain can also depend on the overall hormonal milieu; in the context of low endogenous estrogen or progesterone states in women, testosterone modifies pain sensitivity through descending inhibitory pain pathways (84). In pre-menopausal women at a time of high estrogen levels, progesterone also influences the emotional experience of pain (ie, how unpleasant a stimulus is perceived to be), without affecting the threshold at which the stimulus is regarded as painful (84). The associated symptoms of menopause (notably changes in mood, fatigue, poor sleep, anxiety) can also contribute indirectly to the perception and persistence of pain (13) (figure 4).

Sex steroids have a complex role in inflammation, depending on the context (88), with estrogens being most widely studied (89). Estradiol influences a wide variety of human immune cells, including macrophages, dendritic cells, T cells, and B cells, with estrogen receptors expressed on a number of these, including peripheral blood monocytes (90). High and low estrogen states modulate the production of proinflammatory and antiinflammatory cytokines as well as B cell antibody production (89). Low estrogen levels may be one cause of 'inflamm-ageing', a pro-inflammatory state. High concentrations of E2 and E4 (such as during pregnancy) produce an antiinflammatory state resulting in immune tolerance. However, effects of exogenous estrogen on the immune system may be difficult to measure using existing biomarkers of systemic inflammation. In an RCT in 76 post-menopausal women, no detectable differences in circulating levels of monocyte chemoattractant protein-1 or homocysteine were found in HRT users over 6 months (91). The local effects of sex hormones on joint tissues may be mediated in part via their interactions with inflammatory cytokines, mediators, and growth factors, and their related signalling pathways. For example, estrogen receptors have several kinase phosphorylation sites including the p38 MAP kinases, Akt and src (92). Interpretation of data is difficult, given estrogen receptor signalling can induce or suppress pro-inflammatory cytokine production (89), depending on the cell type, estrogen dose and whether *in vitro* vs *in vivo* (66, 92). One potential mechanism involved is the induction of distinct estrogen receptor-containing transcriptional complexes that differentially activate functional pathways to either promote or inhibit inflammation (93).

The effects of estrogen loss on bone in the context of post-menopausal osteoporosis, and the ability of HRT to counter these effects, are well known. Recently, studies in mice with conditional deletion of the estrogen alpha receptor in bone-forming osteoblasts suggested that reduced subchondral bone mass in these animals was associated with more severe knee osteoarthritis than in intact littermate controls (94). Less is understood about estrogen sensing by other connective tissues, notably articular cartilage, tendon, and muscle (figure 3). Although *in vitro* studies can be conflicting, there is evidence from human studies that post-menopausal women have thinner articular cartilage (95), and that exogenous estrogen use is associated with thicker articular cartilage and intervertebral discs (28, 95, 96). Changes in body composition caused by loss of female sex hormones and related predisposition to obesity also leads indirectly to changes in sex hormone availability, effects on joint tissues, and predisposition to osteoarthritis progression (33).

Like estrogen, testosterone acts directly on connective tissues and indirectly, via aromatisation to estrogens (97, 98). Testosterone deficiency in hypogonadal men is also associated with lower bone mineral density and fractures (99). Lower testosterone levels are also associated with thinner cartilage in men (100). Estrogen and testosterone loss has been shown to contribute to muscle atrophy, whereas exogenous testosterone and to a lesser extent estrogen are anabolic for muscle (23). The effects of sex hormone deficiency

on joint tissues in later life could therefore contribute not only to increased musculoskeletal symptoms but also structural vulnerability of tissues. This in turn could contribute to susceptibility and progression of diseases such as osteoarthritis (figure 4).

Conclusions

Susceptibility to musculoskeletal pain and joint degeneration in osteoarthritis changes with age and with changes in sex hormones over the life-course. There is indisputable evidence for increased susceptibility of women to both musculoskeletal pain and symptomatic osteoarthritis. The evidence that changes in sex hormones affect the development of musculoskeletal pain and osteoarthritis is extensive, albeit largely circumstantial. However, estrogen loss has not been causally linked to the pathogenesis of osteoarthritis; changes in other sex hormones (eg, testosterone, DHEA-S, androstenedione) might be just as important, but this remains poorly understood.

Studying the overall hormonal profile over time is critical to gain a more complete picture of how sex hormones influence pain and musculoskeletal conditions. Rather than absolute hormone levels, it is likely that predisposition to musculoskeletal conditions is more affected by the rate of hormone decline and related accommodation by connective tissues, an idea that is supported by studies in settings where there is sudden and substantial estrogen loss. Whether individuals who experience other aspects of the menopause syndrome are more vulnerable to these problems than are those who pass through menopause quickly or asymptomatically is yet to be understood. Furthermore, whether disease phenotype, such as the site, severity, or trajectory of pain or its resolution differs based on timing relative to menopause or the use of HRT is not known.

A final question is mechanistic and relates to whether effects of sex hormones on musculoskeletal pain or osteoarthritis are primarily direct, mediated by effects on tissues and signalling pathways, or are primarily indirect, via effects on body tissue composition, sleep or mood, or a mixture of both (figure 4).

Sex hormone deficiency remains an unproven potential treatment target for post-menopausal musculoskeletal pain and osteoarthritis (23). It is possible that once disease develops, it may be difficult to modify. A more compelling therapeutic argument might be that exogenous sex hormones could protect against incident disease. Indeed, managing flare or risk on cessation of HRT or other scenarios leading to abrupt estrogen loss could perhaps be more immediate clinical beneficiaries from better knowledge.

Large controlled interventional studies are required to fill knowledge gaps. There is a need for high quality musculoskeletal outcome measures in women's and men's health studies and consideration of reproductive factors and endocrine measurements in musculoskeletal

studies. Increased RCT-level evidence might bring about better therapies for these common rheumatic disorders.

In summary, sex hormones are important for normal musculoskeletal and joint health. Women should be asked about their periods and other menopausal symptoms, and andropause and its symptoms should be considered when assessing men. At present, prescriptions for exogenous hormone therapy should only be considered under their existing licenses, noting that musculoskeletal symptoms may be a part of uncontrolled symptoms of menopause (32).

Search strategy and selection criteria

We predominantly focus our attention on new studies from the last 7 years, reporting on other studies where informative. This builds on previous reviews by us on similar topics in 2016-2018, and excellent reviews by others in this area (13, 20-24). Gender and sex have not been clearly and consistently defined in publications. There are limited studies in transgender individuals. Unless otherwise stated, when using a gendered word we refer here to biological sex.

PubMed was searched for relevant articles from 1 May 2015 – 1 May 2022 relating to cohort, interventional or observational studies using terms including [osteoarthritis OR "OA"] OR [Musculoskeletal pain] OR [chronic widespread pain] OR [arthralgia]. Subsections included terms [estrogen OR "oestrogen" OR "estradiol"] OR ["HRT" OR Hormone OR "Hormone Replacement Therapy"] OR ["selective estrogen receptor modulator" OR "SERM"]. Other subsections included AND [clinical trial] or [RCT] – also set as limiters – OR ["transgender"] OR ["transition"] OR [aromatase inhibitor] OR ["AIMSS"] OR [Oophorectomy] OR [Ovariectomy]. The search was limited to studies in English language.

CONTRIBUTORS

FEW was the primary author. MG, ED, KV and FEW all contributed to the writing, reviewing and editing of the manuscript and all had final responsibility for the decision to submit for publication.

COMPETING INTERESTS

ED reports no competing interests.
MG is supported in part by a scholarship from the Clarendon Fund (Oxford University Press).
KV has received research grant support from Bayer Healthcare. She has received consulting fees from Bayer Healthcare, Grunenthal GmBH and Abbvie. She has received honoraria or speaker fees from Bayer Healthcare, Eli Lilly and Grunenthal GmBH.
FW has received personal consulting fees in 2020 from Pfizer. Her institution received funding until April 2022 from Versus Arthritis for her role as lead of a Versus Arthritis Research Advisory Group.

FUNDING STATEMENT
This article was funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number PB-PG-0416-20023), as part of support for the HOPE-e study. FW is supported by a UKRI Future Leaders Fellowship (MR/S016538/1 and MR/S016538/2) and has also received support from Kennedy Trust for Rheumatology Research and the NIHR Oxford Biomedical Research Centre (BRC) and the NIHR Imperial BRC. FW, ED, KV and MG are all members of the Centre for Osteoarthritis Pathogenesis Versus Arthritis (grant numbers 20205 and 21621) of which FW is a co-applicant. FW is a member of the Centre for Sport, Exercise and Osteoarthritis Research Versus Arthritis (grant number 21595). MG is funded by a Versus Arthritis Clinical Research Fellowship (grant number 21604). ED is funded by NIHR Imperial BRC.
The funding sources had no involvement in the study design, collection, analysis or interpretation of data, or the decision to submit the article for publication.
The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

FIGURE LEGENDS

Figure 1. Biochemistry of sex hormones

The generation and regulation of sex hormones and control of their secretion is complex and includes positive and negative feedback loops. This involves numerous inter-relationships, including sex hormones acting as precursors for one another and altering receptor availability (adapted from Chakraborty et al, 2021). Androgens are precursors to estrogens, converted by aromatase. It is thought that some of the effects of the androgen dehydroepiandrosterone (DHEA) are mediated by its conversion to estradiol. After menopause, estrone dominates, converted by the aromatase enzyme (CYP19A1 within the Cytochrome P(CYP) 450 family) at several sites, in particular adipose tissue.

CYP11A1 (cytochrome P450, family 11, subfamily a, polypeptide 1)/ CP450scc (cytochrome P450 side chain cleavage); CYP17 (Cytochrome P450, 17,20-lyase); 17-OH Pregnenolone (17-hydroxypregnenolone); DHEA (dehydroepiandrosterone); 17β-HSD (17β-hydroxysteroid dehydrogenase); 3β-HSD (3β-hydroxysteroid dehydrogenase); 17-OH Progesterone (17-hydroxyprogesterone); 5-αR (5-alpha reductase); DHT (Dihydrotestosterone); CYP21A1 (cytochrome P450, family 21, subfamily a, polypeptide 1); CYP19A1 (cytochrome P450, family 19, subfamily a, polypeptide 1); CYP11 (Cytochrome P450, family 11); 11β-HSD (11β-hydroxysteroid dehydrogenase)

Figure 2. Changes in sex hormones over life-course

Sex hormones vary markedly between sexes, over time across the lifespan, across the month in females and in pregnancy, and decline during later life, during menopause and andropause or the case of surgical gonadal removal.

Upper panel (females): Menopause is usually defined as the first year after the final menstrual period in women with a uterus who are not using hormonal contraception. Perimenopause spans the onset of menstrual changes and menopausal symptoms, ending one year after the final menstrual period. The mean age of natural menopause worldwide is 49 years, with some geographical variation. FSH levels start to rise for up to 6 years prior to final menstrual period (FMP) and estradiol levels subsequently decline.

Lower panel (males): Though less well characterised than menopause, male andropause is associated with a far more gradual decline in testosterone after the third decade, associated with a rise in FSH and LH.

Different types of exogenous hormones or agents that affect their levels are widely used therapeutically, eg contraceptives or hormone replacement therapy (HRT), and for both benign and malignant conditions at different stages of the life-course. The influence of a low-dose estrogen in the context of HRT can be very different from for example higher estrogen concentrations in the context of oral contraceptive pill, when compared with estrogen at the physiological, cyclical levels seen in menstruating women. This context is important when interpreting the results of clinical studies investigating the mechanistic role of sex hormones in musculoskeletal conditions and pain.

T1, first trimester; T2, second trimester; T3, third trimester; BF, breastfeeding; BF, breastfeeding; BSO, bilateral salpingo-oophorectomy; FSH, follicle stimulating hormone; LH, luteinising hormone; yrs, years

Figure 3. Sites where sex hormones may influence musculoskeletal **pain and osteoarthritis**

Sex hormones have diverse physiological effects and physiological changes in their levels including throughout the life-course, through exogenous replacement or loss can have consequences which may affect the evolution, persistence or amplification/reduction of musculoskeletal pain or painful musculoskeletal conditions such as osteoarthritis. This is summarised in this schematic. The major groups of sex hormones, shown here as estrogens (E), progestogens (P) and androgens (A) can have similar or differing effects, depending on

the system. Tissues where these affects are at play include the central and peripheral nervous systems and various connective tissues present in articular joints.

GABA, γ-aminobutyric acid

Figure 4. Summary: how sex hormone loss during menopause or andropause might influence musculoskeletal **pain and OA**

A number of factors occurring as a direct or indirect result of sex hormone loss (primarily the reduction of estrogen and androgen levels) during menopause or andropause, alongside other processes associated with ageing, may contribute to loss of resilience of musculoskeletal tissues and structural changes which may predispose to conditions such as osteoarthritis. A number of factors associated with sex hormone loss and menopause are known risk factors for chronic painful conditions such as fibromyalgia and may contribute to a person's increased pain vulnerability at this time. The result, for some individuals, may be a 'perfect storm' of factors increasing their risk of painful musculoskeletal conditions. It is proposed that the magnitude and time course of these changes in women as opposed to men may potentially explain some of the relative excess risk of musculoskeletal painful conditions seen in women around and after the age of menopause.

References

1. Versus Arthritis. The State of Musculoskeletal Health 2021: arthritis and other musculoskeletal conditions in numbers. 2021.

2. Arthritis Research UK. Osteoarthritis in General Practice: Data and Perspectives. University of Keele; 2013.

3. Global Burden of Disease Cancer C, Kocarnik JM, Compton K, Dean FE, Fu W, Gaw BL, et al. Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life Years for 29 Cancer Groups From 2010 to 2019: A Systematic Analysis for the Global Burden of Disease Study 2019. JAMA Oncol. 2022;8(3):420-44.

4. Swain S, Sarmanova A, Coupland C, Doherty M, Zhang W. Comorbidities in Osteoarthritis: A Systematic Review and Meta-Analysis of Observational Studies. Arthritis Care Res (Hoboken). 2020;72(7):991-1000.

5. Jones GT, Atzeni F, Beasley M, Fluss E, Sarzi-Puttini P, Macfarlane GJ. The prevalence of fibromyalgia in the general population: a comparison of the American College of Rheumatology 1990, 2010, and modified 2010 classification criteria. Arthritis Rheumatol. 2015;67(2):568-75.

6. Long H, Liu Q, Yin H, Wang K, Diao N, Zhang Y, et al. Prevalence Trends of Site-Specific Osteoarthritis From 1990 to 2019: Findings From the Global Burden of Disease Study 2019. Arthritis Rheumatol. 2022;74(7):1172-83.

7. Prieto-Alhambra D, Judge A, Javaid MK, Cooper C, Diez-Perez A, Arden NK. Incidence and risk factors for clinically diagnosed knee, hip and hand osteoarthritis: influences of age, gender and osteoarthritis affecting other joints. Ann Rheum Dis. 2014;73(9):1659-64.

8. LeResche L, Mancl LA, Drangsholt MT, Saunders K, Von Korff M. Relationship of pain and symptoms to pubertal development in adolescents. Pain. 2005;118(1-2):201-9.

9. Liu B, Balkwill A, Cooper C, Roddam A, Brown A, Beral V, et al. Reproductive history, hormonal factors and the incidence of hip and knee replacement for osteoarthritis in middle-aged women. Ann Rheum Dis. 2009;68(7):1165-70.

10. Ma HL, Blanchet TJ, Peluso D, Hopkins B, Morris EA, Glasson SS. Osteoarthritis severity is sex dependent in a surgical mouse model. Osteoarthritis Cartilage. 2007;15(6):695-700.

11. Chakraborty S, Pramanik J, Mahata B. Revisiting steroidogenesis and its role in immune regulation with the advanced tools and technologies. Genes Immun. 2021;22(3):125-40.

12. van Winden LJ, Vermeulen RFM, van den Noort V, Gaarenstroom KN, Kenter GG, Brood-van Zanten MMA, et al. Changes in Sex Steroids and Relation With Menopausal Complaints in Women Undergoing Risk-reducing Salpingo-oophorectomy. J Endocr Soc. 2022;6(6):bvac069.

13. Watt FE. Musculoskeletal pain and menopause. Post Reprod Health. 2018;24(1):34-43.

14. Aloisi AM, Bonifazi M. Sex hormones, central nervous system and pain. Horm Behav. 2006;50(1):1-7.

15. Rosner IA, Manni A, Malemud CJ, Boja B, Moskowitz RW. Estradiol receptors in articular chondrocytes. Biochem Biophys Res Commun. 1982;106(4):1378-82.

16. Schicht M, Ernst J, Nielitz A, Fester L, Tsokos M, Guddat SS, et al. Articular cartilage chondrocytes express aromatase and use enzymes involved in estrogen metabolism. Arthritis Res Ther. 2014;16(2):R93.

17. Lloyd-Evans E, Waller-Evans H. Biosynthesis and signalling functions of central and peripheral nervous system neurosteroids in health and disease. Essays Biochem. 2020;64(3):591-606.

18. Hetemaki N, Mikkola TS, Tikkanen MJ, Wang F, Hamalainen E, Turpeinen U, et al. Adipose tissue estrogen production and metabolism in premenopausal women. J Steroid Biochem Mol Biol. 2021;209:105849.

19. Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, et al. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. Menopause. 2012;19(4):387-95.

20. Wluka AE, Cicuttini FM, Spector TD. Menopause, oestrogens and arthritis. Maturitas. 2000;35(3):183-99.

21. Richette P, Corvol M, Bardin T. Estrogens, cartilage, and osteoarthritis. Joint Bone Spine. 2003;70(4):257-62.

22. Watt FE. Hand osteoarthritis, menopause and menopausal hormone therapy. Maturitas. 2016;83:13-8.

23. Xiao YP, Tian FM, Dai MW, Wang WY, Shao LT, Zhang L. Are estrogen-related drugs new alternatives for the management of osteoarthritis? Arthritis Res Ther. 2016;18:151.

24. Dennison EM. Osteoarthritis: The importance of hormonal status in midlife women. Maturitas. 2022;165:8-11.

25. Blumel JE, Chedraui P, Baron G, Belzares E, Bencosme A, Calle A, et al. Menopause could be involved in the pathogenesis of muscle and joint aches in mid-aged women. Maturitas. 2013;75(1):94-100.

26. Szoeke CE, Cicuttini FM, Guthrie JR, Dennerstein L. The relationship of reports of aches and joint pains to the menopausal transition: a longitudinal study. Climacteric. 2008;11(1):55-62.

27. Parazzini F, Progretto Menopausa Italia Study G. Menopausal status, hormone replacement therapy use and risk of self-reported physician-diagnosed osteoarthritis in women attending menopause clinics in Italy. Maturitas. 2003;46(3):207-12.

28. Wang YXJ. Menopause as a potential cause for higher prevalence of low back pain in women than in age-matched men. J Orthop Translat. 2017;8:1-4.

29. Eun Y, Yoo JE, Han K, Kim D, Lee KN, Lee J, et al. Female reproductive factors and risk of joint replacement arthroplasty of the knee and hip due to osteoarthritis in postmenopausal women: a nationwide cohort study of 1.13 million women. Osteoarthritis Cartilage. 2022;30(1):69-80.

30. Olaolorun FM, Lawoyin TO. Experience of menopausal symptoms by women in an urban community in Ibadan, Nigeria. Menopause. 2009;16(4):822-30.

31. Islam RM, Bell RJ, Billah B, Hossain MB, Davis SR. Prevalence and severity of vasomotor symptoms and joint pain in women at midlife in Bangladesh: a population-based survey. Menopause. 2016;23(7):731-9.

32. National Institute for Health and Care Excellence (UK). Menopause: diagnosis and management [NG23]. (Last updated: 5 December 2019); 2015.

33. Hussain SM, Wang Y, Giles GG, Graves S, Wluka AE, Cicuttini FM. Female Reproductive and Hormonal Factors and Incidence of Primary Total Knee Arthroplasty Due to Osteoarthritis. Arthritis Rheumatol. 2018;70(7):1022-9.

34. Szoeke CEI, Cicuttini FM, Guthrie JR, Clark MS, Dennerstein L. Factors affecting the prevalence of osteoarthritis in healthy middle-aged women: data from the longitudinal Melbourne Women's Midlife Health Project. Bone. 2006;39(5):1149-55.

35. Dennison EM, Arden NK, Kellingray S, Croft P, Coggon D, Cooper C. Hormone replacement therapy, other reproductive variables and symptomatic hip osteoarthritis in elderly white women: a case-control study. Br J Rheumatol. 1998;37(11):1198-202.

36. Burkard T, Rauch M, Spoendlin J, Prieto-Alhambra D, Jick SS, Meier CR. Risk of hand osteoarthritis in new users of hormone replacement therapy: A nested case-control analysis. Maturitas. 2020;132:17-23.

37. Spector TD, Nandra D, Hart DJ, Doyle DV. Is hormone replacement therapy protective for hand and knee osteoarthritis in women?: The Chingford Study. Ann Rheum Dis. 1997;56(7):432-4.

38. Barnabei VM, Cochrane BB, Aragaki AK, Nygaard I, Williams RS, McGovern PG, et al. Menopausal symptoms and treatment-related effects of estrogen and progestin in the Women's Health Initiative. Obstet Gynecol. 2005;105(5 Pt 1):1063-73.

39. Chlebowski RT, Cirillo DJ, Eaton CB, Stefanick ML, Pettinger M, Carbone LD, et al. Estrogen alone and joint symptoms in the Women's Health Initiative randomized trial. Menopause. 2013;20(6):600-8.

40. Welton AJ, Vickers MR, Kim J, Ford D, Lawton BA, MacLennan AH, et al. Health related quality of life after combined hormone replacement therapy: randomised controlled trial. BMJ. 2008;337:a1190.

41. Cirillo DJ, Wallace RB, Wu L, Yood RA. Effect of hormone therapy on risk of hip and knee joint replacement in the Women's Health Initiative. Arthritis Rheum. 2006;54(10):3194-204.

42. de Klerk BM, Schiphof D, Groeneveld FP, Koes BW, van Osch GJ, van Meurs JB, et al. Limited evidence for a protective effect of unopposed oestrogen therapy for osteoarthritis of the hip: a systematic review. Rheumatology (Oxford). 2009;48(2):104-12.

43. Williams JAE, Chester-Jones M, Minns Lowe C, Goff MV, Francis A, Brewer G, et al. Hormone replacement therapy (conjugated oestrogens plus bazedoxifene) for post-menopausal women with symptomatic hand osteoarthritis: primary report from the HOPE-e randomised, placebo-controlled, feasibility study. Lancet Rheumatol. 2022;4(10):e725-e37.

44. Fujita T, Fujii Y, Munezane H, Ohue M, Takagi Y. Analgesic effect of raloxifene on back and knee pain in postmenopausal women with osteoporosis and/or osteoarthritis. J Bone Miner Metab. 2010;28(4):477-84.

45. Lugo L, Villalvilla A, Largo R, Herrero-Beaumont G, Roman-Blas JA. Selective estrogen receptor modulators (SERMs): new alternatives for osteoarthritis? Maturitas. 2014;77(4):380-4.

46. Scharla S, Oertel H, Helsberg K, Kessler F, Langer F, Nickelsen T. Skeletal pain in postmenopausal women with osteoporosis: prevalence and course during raloxifene treatment in a prospective observational study of 6 months duration. Curr Med Res Opin. 2006;22(12):2393-402.

47. Cowan RM, Ganderton CL, Cook J, Semciw AI, Long DM, Pizzari T. Does Menopausal Hormone Therapy, Exercise, or Both Improve Pain and Function in Postmenopausal Women With Greater Trochanteric Pain Syndrome? A 2 x 2 Factorial Randomized Clinical Trial. Am J Sports Med. 2022;50(2):515-25.

48. Kato Y, Shigehara K, Kawaguchi S, Izumi K, Kadono Y, Mizokami A. Efficacy of testosterone replacement therapy on pain in hypogonadal men with chronic pain syndrome:

A subanalysis of a prospective randomised controlled study in Japan (EARTH study). Andrologia. 2020;52(9):e13768.

49. Basaria S, Travison TG, Alford D, Knapp PE, Teeter K, Cahalan C, et al. Effects of testosterone replacement in men with opioid-induced androgen deficiency: a randomized controlled trial. Pain. 2015;156(2):280-8.

50. Aloisi AM, Bachiocco V, Costantino A, Stefani R, Ceccarelli I, Bertaccini A, et al. Cross-sex hormone administration changes pain in transsexual women and men. Pain. 2007;132 Suppl 1:S60-S7.

51. Levit D, Yaish I, Shtrozberg S, Aloush V, Greenman Y, Ablin JN. Pain and transition: evaluating fibromyalgia in transgender individuals. Clin Exp Rheumatol. 2021;39 Suppl 130(3):27-32.

52. Spector TD, Hart DJ, Brown P, Almeyda J, Dacre JE, Doyle DV, et al. Frequency of osteoarthritis in hysterectomized women. J Rheumatol. 1991;18(12):1877-83.

53. Boer CG, Hatzikotoulas K, Southam L, Stefansdottir L, Zhang Y, Coutinho de Almeida R, et al. Deciphering osteoarthritis genetics across 826,690 individuals from 9 populations. Cell. 2021;184(24):6003-5.

54. Yang Y, Guo T, Liu R, Ke H, Xu W, Zhao S, et al. FANCL gene mutations in premature ovarian insufficiency. Hum Mutat. 2020;41(5):1033-41.

55. Tenti S, Correale P, Cheleschi S, Fioravanti A, Pirtoli L. Aromatase Inhibitors-Induced Musculoskeletal Disorders: Current Knowledge on Clinical and Molecular Aspects. Int J Mol Sci. 2020;21(16).

56. Gagliano-Juca T, Travison TG, Nguyen PL, Kantoff PW, Taplin ME, Kibel AS, et al. Effects of Androgen Deprivation Therapy on Pain Perception, Quality of Life, and Depression in Men With Prostate Cancer. J Pain Symptom Manage. 2018;55(2):307-17 e1.

57. Hyder T, Marino CC, Ahmad S, Nasrazadani A, Brufsky AM. Aromatase Inhibitor-Associated Musculoskeletal Syndrome: Understanding Mechanisms and Management. Front Endocrinol (Lausanne). 2021;12:713700.

58. Henry NL, Azzouz F, Desta Z, Li L, Nguyen AT, Lemler S, et al. Predictors of aromatase inhibitor discontinuation as a result of treatment-emergent symptoms in early-stage breast cancer. J Clin Oncol. 2012;30(9):936-42.

59. Sestak I, Cuzick J, Sapunar F, Eastell R, Forbes JF, Bianco AR, et al. Risk factors for joint symptoms in patients enrolled in the ATAC trial: a retrospective, exploratory analysis. Lancet Oncol. 2008;9(9):866-72.

60. Niravath P. Aromatase inhibitor-induced arthralgia: a review. Ann Oncol. 2013;24(6):1443-9.

61. Moxley G. Rheumatic disorders and functional disability with aromatase inhibitor therapy. Clin Breast Cancer. 2010;10(2):144-7.

62. Shanmugam VK, McCloskey J, Elston B, Allison SJ, Eng-Wong J. The CIRAS study: a case control study to define the clinical, immunologic, and radiographic features of aromatase inhibitor-induced musculoskeletal symptoms. Breast Cancer Res Treat. 2012;131(2):699-708.

63. Robarge JD, Duarte DB, Shariati B, Wang R, Flockhart DA, Vasko MR. Aromatase inhibitors augment nociceptive behaviors in rats and enhance the excitability of sensory neurons. Exp Neurol. 2016;281:53-65.

64. Ockene JK, Barad DH, Cochrane BB, Larson JC, Gass M, Wassertheil-Smoller S, et al. Symptom experience after discontinuing use of estrogen plus progestin. JAMA. 2005;294(2):183-93.

65. Speer LM, Mushkbar S, Erbele T. Chronic Pelvic Pain in Women. Am Fam Physician. 2016;93(5):380-7.

66. Sniekers YH, Weinans H, Bierma-Zeinstra SM, van Leeuwen JP, van Osch GJ. Animal models for osteoarthritis: the effect of ovariectomy and estrogen treatment - a systematic approach. Osteoarthritis Cartilage. 2008;16(5):533-41.

67. Oestergaard S, Sondergaard BC, Hoegh-Andersen P, Henriksen K, Qvist P, Christiansen C, et al. Effects of ovariectomy and estrogen therapy on type II collagen degradation and structural integrity of articular cartilage in rats: implications of the time of initiation. Arthritis Rheum. 2006;54(8):2441-51.

68. von Loga IS, Batchelor V, Driscoll C, Burleigh A, Chia SL, Stott B, et al. Does Pain at an Earlier Stage of Chondropathy Protect Female Mice Against Structural Progression After Surgically Induced Osteoarthritis? Arthritis Rheumatol. 2020;72(12):2083-93.

69. Gordon FT, Soliman MR. The effects of estradiol and progesterone on pain sensitivity and brain opioid receptors in ovariectomized rats. Horm Behav. 1996;30(3):244-50.

70. Kuba T, Wu HB, Nazarian A, Festa ED, Barr GA, Jenab S, et al. Estradiol and progesterone differentially regulate formalin-induced nociception in ovariectomized female rats. Horm Behav. 2006;49(4):441-9.

71. Aloisi AM, Ceccarelli I, Fiorenzani P. Gonadectomy affects hormonal and behavioral responses to repetitive nociceptive stimulation in male rats. Ann N Y Acad Sci. 2003;1007:232-7.

72. Lesnak JB, Inoue S, Lima L, Rasmussen L, Sluka KA. Testosterone protects against the development of widespread muscle pain in mice. Pain. 2020;161(12):2898-908.

73. Freitas RP, Lemos TM, Spyrides MH, Sousa MB. Influence of cortisol and DHEA-S on pain and other symptoms in post menopausal women with fibromyalgia. J Back Musculoskelet Rehabil. 2012;25(4):245-52.

74. Marinelli A, Prodi A, Pesel G, Ronchese F, Bovenzi M, Negro C, et al. Serum dehydroepiandrosterone sulphate, psychosocial factors and musculoskeletal pain in workers. Occup Med (Lond). 2017;67(9):684-6.

75. de Kruijf M, Stolk L, Zillikens MC, de Rijke YB, Bierma-Zeinstra SMA, Hofman A, et al. Lower sex hormone levels are associated with more chronic musculoskeletal pain in community-dwelling elderly women. Pain. 2016;157(7):1425-31.

76. Hussain SM, Cicuttini FM, Bell RJ, Robinson PJ, Davis SR, Giles GG, et al. Incidence of total knee and hip replacement for osteoarthritis in relation to circulating sex steroid hormone concentrations in women. Arthritis Rheumatol. 2014;66(8):2144-51.

77. Sowers MF, Hochberg M, Crabbe JP, Muhich A, Crutchfield M, Updike S. Association of bone mineral density and sex hormone levels with osteoarthritis of the hand and knee in premenopausal women. Am J Epidemiol. 1996;143(1):38-47.

78. Tajar A, McBeth J, Lee DM, Macfarlane GJ, Huhtaniemi IT, Finn JD, et al. Elevated levels of gonadotrophins but not sex steroids are associated with musculoskeletal pain in middle-aged and older European men. Pain. 2011;152(7):1495-501.

79. Livshits G, Macgregor AJ, Gieger C, Malkin I, Moayyeri A, Grallert H, et al. An omics investigation into chronic widespread musculoskeletal pain reveals epiandrosterone sulfate as a potential biomarker. Pain. 2015;156(10):1845-51.

80. Hussain SM, Cicuttini FM, Giles GG, Graves SE, Wang Y. Relationship between circulating sex steroid hormone concentrations and incidence of total knee and hip arthroplasty due to osteoarthritis in men. Osteoarthritis Cartilage. 2016;24(8):1408-12.

81. Kerkhof HJ, Meulenbelt I, Carr A, Gonzalez A, Hart D, Hofman A, et al. Common genetic variation in the Estrogen Receptor Beta (ESR2) gene and osteoarthritis: results of a meta-analysis. BMC Med Genet. 2010;11:164.

82. Vincent K, Tracey I. Hormones and their Interaction with the Pain Experience. Rev Pain. 2008;2(2):20-4.

83. Vincent K, Tracey I. Sex hormones and pain: the evidence from functional imaging. Curr Pain Headache Rep. 2010;14(5):396-403.

84. Vincent K, Warnaby C, Stagg CJ, Moore J, Kennedy S, Tracey I. Brain imaging reveals that engagement of descending inhibitory pain pathways in healthy women in a low endogenous estradiol state varies with testosterone. Pain. 2013;154(4):515-24.

85. Dawson-Basoa ME, Gintzler AR. Estrogen and progesterone activate spinal kappa-opiate receptor analgesic mechanisms. Pain. 1996;64(3):608-15.

86. Linnstaedt SD, Mauck MC, Son EY, Tungate AS, Pan Y, Rueckeis C, et al. Peritraumatic 17beta-estradiol levels influence chronic posttraumatic pain outcomes. Pain. 2021;162(12):2909-16.

87. Carvalho B, Angst MS, Fuller AJ, Lin E, Mathusamy AD, Riley ET. Experimental heat pain for detecting pregnancy-induced analgesia in humans. Anesth Analg. 2006;103(5):1283-7.

88. Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol. 2016;16(10):626-38.

89. Straub RH. The complex role of estrogens in inflammation. Endocr Rev. 2007;28(5):521-74.

90. Phiel KL, Henderson RA, Adelman SJ, Elloso MM. Differential estrogen receptor gene expression in human peripheral blood mononuclear cell populations. Immunol Lett. 2005;97(1):107-13.

91. Tasci T, Sukur YE, Ozmen B, Atabekoglu CS, Cengiz SD, Kocbulut E, et al. Effects of transdermal and oral hormone replacement therapies on monocyte chemoattractant protein-1 levels: a randomized clinical trial. Eur J Obstet Gynecol Reprod Biol. 2014;176:50-4.

92. Roman-Blas JA, Castaneda S, Largo R, Herrero-Beaumont G. Osteoarthritis associated with estrogen deficiency. Arthritis Res Ther. 2009;11(5):241.

93. Safe S, Kim K. Non-classical genomic estrogen receptor (ER)/specificity protein and ER/activating protein-1 signaling pathways. J Mol Endocrinol. 2008;41(5):263-75.

94. Ziemian SN, Ayobami OO, Rooney AM, Kelly NH, Holyoak DT, Ross FP, et al. Low bone mass resulting from impaired estrogen signaling in bone increases severity of load-induced osteoarthritis in female mice. Bone. 2021;152:116071.

95. Wluka AE, Davis SR, Bailey M, Stuckey SL, Cicuttini FM. Users of oestrogen replacement therapy have more knee cartilage than non-users. Ann Rheum Dis. 2001;60(4):332-6.

96. Baron YM, Brincat MP, Galea R, Calleja N. Intervertebral disc height in treated and untreated overweight post-menopausal women. Hum Reprod. 2005;20(12):3566-70.

97. Rastrelli G, Carter EL, Ahern T, Finn JD, Antonio L, O'Neill TW, et al. Development of and Recovery from Secondary Hypogonadism in Aging Men: Prospective Results from the EMAS. J Clin Endocrinol Metab. 2015;100(8):3172-82.

98. Wu FC, Tajar A, Beynon JM, Pye SR, Silman AJ, Finn JD, et al. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med. 2010;363(2):123-35.

99. Mohamad NV, Soelaiman IN, Chin KY. A concise review of testosterone and bone health. Clin Interv Aging. 2016;11:1317-24.

100. Cicuttini FM, Wluka A, Bailey M, O'Sullivan R, Poon C, Yeung S, et al. Factors affecting knee cartilage volume in healthy men. Rheumatology (Oxford). 2003;42(2):258-62.