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The musculoskeletal syndrome of menopause

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ABSTRACT

Fifty-one percent of humans are born with ovaries. As the ovarian production of estrogen diminishes in midlife and ultimately stops, it is estimated that more than 47 million women worldwide enter the menopause transition annually. More than 70% will experience musculoskeletal symptoms and 25% will be disabled by them through the transition from perimenopause to postmenopause. This often-unrecognized collective of musculoskeletal symptoms, largely influenced by estrogen flux, includes arthralgia, loss of muscle mass, loss of bone density and progression of osteoarthritis, among others. In isolation, it can be difficult for clinicians and patients to adequately appreciate the substantial role of decreasing estrogen, anticipate the onset of related symptoms and actively treat to mitigate future detrimental processes. Thus, in this review we introduce a new term, the musculoskeletal syndrome of menopause, to describe the collective musculoskeletal signs and symptoms associated with the loss of estrogen. Given the significant effects of these processes on quality of life and the associated personal and financial costs, it is important for clinicians and the women they care for to be aware of this terminology and the constellation of musculoskeletal processes for which proper risk assessment and prophylactic management are of consequence.

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Musculoskeletal system; menopause; perimenopause; estrogen deficiency

Introduction

Approximately 2 million women in the USA and more than 47 million women worldwide will enter menopause annually, reaching this transition between ages 45 and 55 years on average with a duration of symptoms lasting 2–10 years [1,2]. More than 35 symptoms are known to be associated with menopause, including hot flashes, brain fog, sleep disturbances, anxiety and loss of libido; however, musculoskeletal symptoms are less commonly recognized by clinicians or patients and can be silent, devastating and permanent unless addressed.

Clinician awareness of the musculoskeletal syndrome of menopause is critical as an estimated 70% of all midlife women will experience the musculoskeletal syndrome of menopause, 25% will experience severe symptoms and 40% will have no structural findings [3]. The musculoskeletal syndrome of menopause is a term being introduced here to describe the typical symptoms impacted by the precipitous drop in estrogen surrounding the menopause transition. Understanding the role of diminished estrogen in the musculoskeletal systems of midlife women will enable clinicians to provide more complete guidance and increase patient satisfaction. The musculoskeletal syndrome of menopause includes, but is not limited to, musculoskeletal pain, arthralgia, loss of lean muscle mass, loss of bone density with increased risk of resultant fracture, increased tendon and ligament injury, adhesive capsulitis and cartilage matrix fragility with the progression of osteoarthritis.

The musculoskeletal syndrome of menopause may have a profound negative impact on the quality of life of postmenopausal women. Women and clinicians alike should thus be versed in the recognition and treatment of these problems. In this review, we introduce new terminology, discuss the importance of comprehension of the musculoskeletal syndrome of menopause and stress the importance of prevention and active treatment of this syndrome in postmenopausal women.

The significance of proper terminology in a similar estrogen-related process can be found concerning the genitourinary syndrome of menopause, which consists of genital symptoms including dryness, burning and irritation, sexual symptoms including lack of lubrication, discomfort or pain and impaired function, as well as urinary symptoms including urgency, dysuria and recurrent urinary tract infections [4,5]. Due to the lack of clarity regarding the menopausal effects of previously used terminology such as vulvovaginal atrophy and atrophic vaginitis, the Board of Directors of the International Society for the Study of Women's Sexual Health and the Board of the North American Menopause Society officially approved the term genitourinary syndrome of menopause in 2014 [5]. It is evident that the precedent set by the genitourinary syndrome of menopause is that of increasing awareness of decreasing estrogen-related states to provide more comprehensive care for patients and give

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women a more encompassing term to understand their physiological changes.

Musculoskeletal syndrome of menopause

The overall prevalence of musculoskeletal pain in perimenopausal women is approximately 71%, with perimenopausal women demonstrating a higher risk for musculoskeletal pain than their premenopausal counterparts [3]. These patients' imaging results may show no structural findings; however, it is important to be conscious of the hormonal changes that occur in this cohort, especially related to estrogen. Often the primary point of contact in the care of these patients with musculoskeletal ailments, orthopedic surgeons should be aware of the musculoskeletal changes associated with menopause since they can have permanent and devastating consequences including bone loss, muscle loss, muscle weakness, frailty and fractures, and metabolic dysfunction. Primary care physicians and obstetrics and gynecology practitioners, on the other hand, may be the first point of contact in the early phases before musculoskeletal symptoms present. In these cases, conversations with women about the musculoskeletal syndrome of menopause at regular check-ups or appointments to discuss other common perimenopausal complaints, including hot flashes, may be beneficial for preventative care.

The National Institutes of Health defines menopause as a point in time 12 months after a woman's last period and perimenopause, or the menopausal transition, as the years leading up to that point when women may have changes in their monthly cycles, hot flashes or other symptoms. The average age for onset of perimenopause is 47.5 years [6], while the average age of menopause is 52.6 ± 2.5 years, with Hispanics having an onset approximately 2 years earlier [7].

During perimenopause, women have an average reduction of 10% in bone mineral density [8]. Furthermore, women have a reduction of 0.6% in muscle mass per year after menopause [9]. These musculoskeletal issues can be attributed to the decline in estradiol, the most biologically active form of estrogen, which impacts nearly all types of musculoskeletal tissue including bone, tendon, muscle, cartilage, ligament and adipose [10,11]. The fall in estradiol levels leads to five primary changes (Table 1): an increase in inflammation, a decrease in bone mineral density leading to osteopenia/osteoporosis, arthritis, sarcopenia and a decrease in the proliferation of satellite cells (muscle stem cells).

Table 1. Musculoskeletal syndrome of menopause: processes and signs.

Process	*Signs*
Inflammation	Arthralgia, joint pain, joint discomfort, frozen shoulder
Sarcopenia	Poor balance, falls, decreased muscle mass, loss of stamina, walking slowly
Decreased satellite cell proliferation	Decreased muscle mass, inability to gain muscle
Osteoporosis	Loss of height, back pain, stooped posture, low-impact fracture
Arthritis	Arthralgia, joint pain, joint stiffness

Inflammation

Estrogen is an inflammatory regulator that plays a role in the prevention of generalized arthralgia, the subjective experience of joint pain. The pain experienced increases across the menopausal transition, peaking in early postmenopause, and often has no specific magnetic resonance imaging findings and may not require specific intervention. Nevertheless, more than half of perimenopausal women report arthralgia symptoms [12,13]. There is also evidence to support increased arthralgia reporting in postmenopausal women compared with premenopausal women and similar results have been found in patients who experience sudden withdrawal of menopausal hormone therapy (MHT) or aromatase inhibitors [14,15]. The regulation of inflammation occurs via 17β-estradiol, which inhibits the release of inflammatory cytokine TNF-α [16], which can degrade muscle proteins and reduce the ability of the adult muscle to respond to damage [17]. TNF-α is released by adipocytes and can promote the accumulation of fat mass and impair muscle function [18–20]. Estrogen replacement therapy can attenuate fat gain and decrease lean muscle loss [21,22], with evidence that estrogen acts and influences adipose tissue through estrogen receptor-α [18].

Estrogen is a potent anti-inflammatory factor modulated by the inflammasome, an element of the innate immune system [23,24]. The inflammasome is a multiprotein complex that activates caspase-1 and processes pro-inflammatory cytokines such as IL-1β and IL-18 [25,26]. Moreover, there is increasing and compelling evidence that inflammasome is modulated by estrogen receptor-β [27]. Since estrogen can be used to inhibit the inflammation-mediated release of pro-inflammatory cytokines and regulate the inflammasome, MHT is an interesting alternative to ameliorate symptoms.

Sarcopenia

Sarcopenia, or age-related loss of lean muscle mass, is characterized by atrophy of fast muscle fibers, loss of type II fibers, decreased number of motor units and increased intramuscular adipose tissue [28]. According to the updated definitions from the European Working Group on Sarcopenia in Older People, sarcopenia is probable when low muscle strength is detected, diagnosed when the quantity or quality of muscle is low and considered severe when low muscle strength, low muscle quantity or quality and low physical performance are all present [29]. Regarding possible interventions to attenuate sarcopenia, it is suggested that nutritional interventions, including intake of proteins, vitamin D and creatine, as well as exercise including resistance training, may improve muscle mass and strength, although more high-quality studies are needed [30].

Estrogen has important functions related to muscle mass and strength. It has been shown that the decline in estrogen through ovariectomy in animals leads to a decrease in mitochondrial function, membrane microviscosity, and complex I and I+III activity [31]. Moreover, the decline in estrogen leads to increased mitochondrial H_2O_2 production [32], decreased levels of antioxidant proteins [32,33] and impaired insulin

sensitivity [31]. These changes occur due to estrogen's capacity to restore cellular redox and glucose homeostasis in skeletal muscle [31,34,35]. There is evidence for estrogen being beneficial to muscle mass and strength in animal models [36,37]. In one experiment, 24 weeks of estrogen deficiency resulted in a 10% decrease in strength that corresponded with an 18% decrease in fiber cross-sectional area [36]. In another experiment with ovariectomized mice, it was suggested that in the absence of estrogen, muscle is more prone to injury and regrowth is limited [37].

Aging in perimenopause and postmenopause is another factor that contributes to decreased muscle mass and strength. It has been shown that postmenopausal women experience a rapid decrease in muscle mass and strength and, thus, are more vulnerable to age-related frailty [38]. To counteract such losses, MHT is a plausible method, especially when paired with resistance training [39,40]. In a cross-sectional study involving postmenopausal women, it was found that muscle cross-sectional area and grip strength were greater in estrogen replacement therapy users than in non-users [41]. Furthermore, it is suggested that MHT can help improve sensitivity to anabolic stimuli since it was found that protein synthesis increased significantly following resistance training [42].

Satellite cell proliferation

Satellite cells, stem cells located on muscle fibers, promote plasticity and regeneration [43]. Type I oxidative fibers have much higher numbers of satellite cells due to their better blood supply [43]. Satellite cells are quiescent in a steady state [44,45], but following injury or anabolic stimulation are activated to repair muscle tissue in chronic inflammatory states [46,47]. Estradiol stimulates the activation and proliferation of the satellite cells through estrogen receptors [48] and part of the force generated by skeletal muscle appears to be determined by the binding of estradiol to estrogen receptor-α [49,50]. By losing the stimulation that estrogen promotes by binding to estrogen receptor-α, muscle strength and recovery after injury are impaired.

Although limited research exists quantifying satellite cells in postmenopausal women, Collins et al. recently took a mechanistic approach to investigate this phenomenon in a murine model. Compared to control mice, ovariectomized mice were found to have 30–60% fewer satellite cells, specifically with decreased concentrations in the tibialis anterior, and the reduction was associated with the duration of the hormone deficiency [49]. This finding was consistent in other muscles including the extensor digitorum longus, gastrocnemius and diaphragm, although the soleus, comparatively more difficult to fatigue, was unaffected by hormonal changes. Along with risk reduction, postmenopausal osteoporosis management guidelines typically include strengthening the muscles around areas of weaker bone, especially around the back, hips and lower legs. These data suggest that, without replacement therapy, a decrease in satellite cells may compound osteopenia/osteoporosis and increase frailty due to difficulty in generating muscle power and adequate regeneration.

Bone density

Osteoporosis is a serious problem with 200 million postmenopausal women affected worldwide [51]. It is underdiagnosed, preventable and treatable. Between 30% and 50% of women suffer a clinical fracture in their life and 70% of hip fractures occur in women [51]. Osteoporotic fractures are extremely detrimental since they can lead to chronic pain, deformity, disability and even death [52]. Osteoporosis is diagnosed based on bone mineral density assessment using a dual-energy X-ray absorptiometry scan, while the 10-year probability of fracture in a patient with osteoporosis can be estimated using the Fracture Risk Assessment Tool (FRAX) score [53]. A FRAX score is calculated using demographic data, important clinical risk factors such as smoking, corticosteroid use and history of rheumatoid arthritis, as well as an optional input of bone mineral density data obtained from a dual-energy X-ray absorptiometry scan [54].

Estrogen deficiency is associated with significant bone loss [21], increasing fragility and risk of fracture. The prevention of osteoporosis includes appropriate nutrition and exercise and the removal of risk factors. Furthermore, it has been shown that MHT was adequate and effective in the prevention of osteoporotic fractures in at-risk women [55]. Treatment with MHT in postmenopausal women was able to preserve or increase bone mineral density at all skeletal locations [55]. Further, it has been demonstrated that MHT can decrease the incidence of osteoporotic fractures [56–59]. Therefore, MHT should be indicated for the prevention and treatment of osteoporotic fractures due to its evidence of effectiveness, cost and safety [60]. Future research needs to be conducted to determine the dosing thresholds and efficacy of MHT in managing osteoporosis in various age-specific cohorts of postmenopausal women.

Cartilage damage and osteoarthritis

Cartilage is composed of a dense extracellular matrix and highly specialized chondrocytes, cells that are partly regulated by estrogen [61]. While both mechanical and biochemical factors contribute toward the osteoarthritis progression, it is understood that osteoarthritis incidence in women increases dramatically around the time of menopause and recent literature claims that women experience more debilitating arthritic pain than men [62–64]. In a comprehensive review of estrogen and osteoarthritis by Richette et al. a possible association was suggested between menopausal estrogen deprivation and the frequency of knee, hip and finger osteoarthritis and severity of hip osteoarthritis [65].

The subject of MHT in the prevention and treatment of osteoarthritis in postmenopausal women is controversial. There is evidence that estrogen has protective and mitogenic properties in intervertebral disks [66] and that the estrogen decrease during menopause leads to changes in the connective tissue matrix which may be prevented by estrogen replacement therapy [67]. In an ovariectomized rat model for osteoarthritis, Xu et al. found that estrogen therapy reduced the extent of cartilaginous degeneration and resorption of subchondral bone in estrogen-deficiency [68]. However, a recent meta-analysis found

a significant positive association between the use of MHT and joint replacement [69]. Further research is necessary to determine whether there is a specific age range or dosage for which MHT may be beneficial for osteoarthritis.

Clinical applications

Given the variety of negative implications on women's health, and specifically the musculoskeletal system, associated with estrogen depletion during menopause, it is important for both practitioners and patients to be cognizant of prevention and management approaches. Conservative approaches include testing, nutrition and exercise. Updated guidelines recommend osteoporosis screening for women aged 65 years or older and for those aged 50–64 years who have certain risk factors, including a positive family history of osteoporosis [70]. Nutritional vitamin D has been shown to effectively improve hip bone mineral density in postmenopausal women and reduce the incidence of falls [71,72]. A recent randomized, double-blind, placebo-controlled trial investigating isolated vitamin D supplementation on bone turnover markers in postmenopausal women aged 50–65 years with vitamin D deficiency found that 1000 IU of vitamin D3 for 9 months was associated with reduced bone turnover markers, suggesting the relationship between proper nutritional supplementation and decreased bone loss in these patients [73]. Intrinsically linked with vitamin D in phosphorus–calcium metabolism is magnesium, which is necessary for the functioning of parathyroid hormone and suggested by several authors to improve postmenopausal musculoskeletal symptoms [74–77]. A recent randomized controlled trial of 52 postmenopausal women aged between 44–76 years found that daily treatment with 500 mg of magnesium resulted in significantly increased vitamin D levels [74]. More research is needed to determine protocols and strategies to maximize the benefit of magnesium supplementation and determine which patient parameters should guide treatment.

Another vitamin supplementation that may decrease the progression and treat osteoporosis is vitamin K2. A recent meta-analysis by Zhou et al. of nine randomized controlled trials consisting of a total of 6853 postmenopausal patients with osteoporosis found a significantly increased change in lumbar and forearm bone mineral density without evidence of serious adverse effects related to the supplementation [78]. Further research is necessary to determine whether supplementation of these two vitamins in premenopausal or perimenopausal patients before the onset of osteoporosis, or during the transition to osteopenia, is effective.

Among the various prevention and treatment approaches associated with menopause, exercise is perhaps the only non-controversial modality. Decreasing estrogen is associated with loss of type II muscle fibers and subsequently decreased power, which has been suggested as the primary measure for completing activities of daily living [79–81]. Although there is at present a lack of concrete evidence among postmenopausal women regarding optimal weight training, it is generally acknowledged that resistance training with heavier weights in lower repetition sets tends to increase muscular power more effectively than training with lighter weights in higher repetition sets [82]. Along with dietary changes, including increased protein intake and the aforementioned vitamins, resistance exercise may be critical for postmenopausal women to decrease their risk of falls and fractures. Other supplements are currently being investigated in tandem with resistance training in the postmenopausal female, including creatine which has shown positive bone mineral density and muscle power results in preliminary research [83].

MHT is perhaps the next frontier in the treatment of postmenopausal women in general, and particularly for the musculoskeletal syndrome of menopause. By slowing the rate of estrogen loss, MHT offers a unique modality to mitigate the potentially devastating musculoskeletal effects of estrogen withdrawal and allows for a smoother physiological transition. MHT is typically administered with estradiol and progestogens, the latter of which is included if the patient has a uterus. Systemic MHT may be administered via pills, transdermal patches or sprays depending on patient and clinician preference. Given that perimenopausal patients often present with musculoskeletal symptoms without positive imaging, physicians must be aware of the musculoskeletal syndrome of menopause, communicate the potential role of MHT and lifestyle interventions in their management, and potentially refer them to a specialist who can guide these plans.

The role of the clinician in managing the musculoskeletal syndrome of menopause should not be overlooked, especially among orthopedic surgeons who may be less familiar with the musculoskeletal manifestations of estrogen decline than primary care and obstetrics and gynecology physicians. For example, when midlife women present with symptoms of adhesive capsulitis or atraumatic joint pain, or describe recent loss of muscle or height, the adept physician should introduce the musculoskeletal syndrome of menopause and encourage their agency in treatment. Nevertheless, it remains clinically imperative that each woman deserves a thorough clinical evaluation for structural damage or other pathologies that may explain the presenting symptomatology and contribute to the overall picture, which may in part be influenced by estrogen deficiency. However, clinicians should keep the physiologic effects of estrogen on the musculoskeletal system centered in their care plans in perimenopausal and postmenopausal patient populations. Psychologically, this may increase patient satisfaction by reassuring them that their condition is normal due to expected biochemical changes and, more substantially, that these changes are treatable and that proper steps can be taken immediately to prevent further manifestations. This approach to care is in stark contrast to common adages told to the perimenopausal patient including 'it is time to start slowing down' and 'this tends to happen as women age', non-descript sentiments that offer little value in the management of common musculoskeletal conditions in this cohort.

Conclusions

The musculoskeletal syndrome of menopause is a novel nomenclature to describe the common musculoskeletal

symptoms related to loss of estrogen levels, including joint pain, inflammation, sarcopenia, osteoporosis and cartilage damage. In isolation, these terms do not adequately communicate to patients the role of decreasing estrogen or suggest how treatment with proper nutrition, resistance training, vitamin intake and/or MHT may have a substantial role in quality of life, preventing falls and decreasing frailty mortality.

Physicians should embrace this terminology as a means of expressing understanding to patients, instilling agency that may increase patient satisfaction and offering appropriate active treatment to give more comprehensive care. More broadly, recognition of this terminology is important to stimulate research interest. Multiple salient clinical research questions remain regarding optimal management and prevention, including the potential prevention of multiple entities in the musculoskeletal syndrome of menopause with early MHT, such as the rapid progression of arthritis, acute worsening of arthralgia, frozen shoulder and loss of skeletal muscle mass. Investigations to determine the minimum effective dosing regimens for this preventive approach are also outstanding, as is re-evaluating the current standard of diagnosing osteoporosis at age 65 years with a dual-energy X-ray absorptiometry scan versus earlier screening. In the meantime, it is prudent for physicians to complete detailed history and physical examinations to identify early-onset or increased susceptibility to developing future ailments, utilize prevention recommendations of dietary and exercise modifications, vitamin supplementation and MHT, as well as discuss the musculoskeletal syndrome of menopause early and thoroughly to best prepare patients. Answering the myriad of questions that remain in understanding the mechanisms, prevention of and treatments for the musculoskeletal syndrome of menopause may profoundly change the health and quality of life of the millions of women transitioning through menopause worldwide.

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