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The Role of Sex Differences in Musculoskeletal Tissues and Disease

Musculoskeletal diseases impact men and women differently. Hormones, genetics, anatomical differences, and psychosocial factors can influence an individual’s risk for developing a musculoskeletal disease, how it presents, and their clinical outcomes.1 This paper will discuss the impacts of sex differences on the structure and function of musculoskeletal tissues within the context of sex as a biological variable (SABV) research. Keeping with convention, sex refers to biological differences that result in being male or female, and gender refers to the complex psychosocial interactions of biological, societal, and environmental influences.2

*Sex as a Biological Variable*

Research on women’s health has primarily focused on the reproductive system during the reproductive years; however, research on sex and gender differences on other systems has grown in the past 30 years.3 Historical failure to include women as subjects and analyzing the role of biological sex across biomedical research lead to clinical decisions for female patients based on observations in men. To address this discrepancy, the National Institutes of Health (NIH) implemented their SABV policy in 1994 that requires the inclusion of women in clinical research studies and results analysis based on sex and gender in all NIH-funded studies.3 Still, less than one-third of published NIH-funded studies analyze data by sex.4 Despite the slow progress, there continue to be renewed calls for this research across disciplines. Fortunately, sex differences research for musculoskeletal conditions has expanded over the past 10 years.1

It is critical that clinicians understand how sex differences impact body systems since 55.8% of patients seen by physical therapists are females.5 Many musculoskeletal conditions such as degenerative joint disease, connective tissue disorders, and osteoporotic fractures are more common in women and are managed by physical therapists.5 Still, research and education on sex differences within physical therapy is limited.2 Understanding how sex and gender influence a patient’s presentation, response to treatment, and outcomes is an opportunity for further development within the profession.

 *Overview of Hormones and their Impacts on Musculoskeletal Tissues*

 Estrogen is the primary sex hormone in women. In the ovaries, aromatase converts testosterone into estradiol (E2), its active form, which is secreted in varying concentrations during the menstrual cycle.6 To stimulate ovulation, E2 levels can increase 10-100 times above baseline concentrations, in coordination with the other reproductive hormones, including follicle stimulating hormone (FSH), luteinizing hormone (LH), and progesterone.6 Many women use hormonal contraception (COC) which typically provide a daily low-level dose of E2 and progestin to prevent ovulation, and thus prevent pregnancy. At menopause, menses stops, and plasma estradiol and progesterone levels are low.6 A graph of these hormonal fluctuations are in Figure 1. Sex hormones pass through the cell membrane and bind to receptors in musculoskeletal tissues, impacting their structure and function.6 Generally, E2 and progesterone work in opposition to maintain homeostasis, so altering their relative concentrations can have implications for these tissues.

 For example, depot medroxyprogesterone acetate injection has been associated with a decrease in bone mineral density (BMD) and an increase in fracture risk.7 While these risks must be balanced against its effectiveness and utility, the FDA now recommends this method should not be used longer than two years.8 Lopez et al. found that COCs do not appear to negatively impact BMD overall, but the variations in formula and hormone concentrations had differing effects on BMD.7 However, Raine-Bennett et al. found that oral contraceptive use, both COC and progestin-only, was protective against fracture due to E2’s inhibitory effects on bone resoprtion.8 In the ligaments, COC use can reduce injury risk by decreasing relaxin and E2 concentrations, leading to a relatively higher concentration of progesterone.9 Monophasic COCs had a greater protective effect against injury risk than triphasic COCs because the triphasics lead to lower levels of progesterone.9 Thus, it’s critical that physical therapists inquire about type, dose, route of administration, and duration of use if the patient uses hormonal contraceptives since they impact tissues differently.

In menopausal and post-menopausal women, hormone replacement therapy (HRT), a combination of E2 and medroxyprogesterone, has wide-ranging risks and benefits. It is typically prescribed to relieve the uncomfortable symptoms of menopause and also has the benefit of decreasing the risk of fractures and some cancers.10 This is likely due to the increased circulatory concentrations of E2. Unfortunately, HRT can also increase the long-term risk of coronary artery disease, breast cancer and stroke.10 Consequently, the American Academy of Family Physicians recommends against using HRT to prevent chronic health conditions.10 Understanding the function of sex hormones on musculoskeletal tissues is key to understanding differences in disease risk and outcomes.

*Bone*

 Bone is constantly remodeled throughout the lifespan in order to become stronger, denser, and more resilient to soft tissue forces. Peak BMD for occurs between the ages of 16-40, and dramatically declines thereafter.11,12 Two primary cell types, osteoblasts and osteoclasts, are responsible for the remodeling process. Osteoblasts increase bone matrix, whereas osteoclasts degrade bone and allow its minerals to be reabsorbed through the blood stream.13 The balance in terms of number and activity of these cells, called turnover, leads to a net gain or loss of the bone quantity, quality, and density. Ideally, rates of resorption and formation should occur equally to maintain a constant level of BMD with adjustments to accommodate growth and injury.

 Estrogen plays an important role in the turnover rate of bone. When E2 binds to its receptors in bone, it inhibits pro-osteoclastic cytokines and induces osteoclastic apoptosis, reducing the number of osteoclasts in the bone.14 It also promotes the production of osteoblasts and regulates proteins that induce osteoblast apoptosis.14 Thus, the binding of E2 to the bone produces a net positive for osteoblastic activity, resulting in stronger, denser bone. While there is less research available on its role, progesterone works with E2 to increase BMD by stimulating new osteoblast formation and increased levels of bone matrix.12 Post-menopausal women have a dramatically increased rate of bone turnover from the lower levels of these hormones which negatively impacts the bone’s mineralization, collagen composition and orientation, and the accumulation of microfractures.11

A reduction in BMD predisposes the bone to increased risk of fracture since it has less resistance to multidirectional forces and circulating concentrations of E2 can be used to predict fracture risk. Total E2 levels that are <5 pg/ml are associated with a 2.5x increased risk in vertebral body and hip fractures in post-menopausal women regardless of their age and size.15 Thus, researchers have proposed using estrogen supplementation therapeutically to prevent bone-loss related disorders. A 2017 Cochrane Review showed that HRT with estrogen is effective for preventing osteoporosis, but that the risks often do not outweigh the benefits.16 In women with Functional Hypothalamic Amenorrhea, an endocrine disorder that results in reduced E2 levels, taking a COC pill resulted in a significant 3.3% increase in BMD in the lumbar spine, but not in other sites.17 Clearly, having optimal levels of E2 is essential for bone health and preventing fractures; however the multi-system effects of estrogen may make it an inappropriate therapeutic option due to the risks to other body systems.

Osteoporosis is a skeletal disorder that occurs at four times the rate in women as in men and is characterized by reduced bone density, increasing the individual’s risk for fracture.18 Physical therapists play a key role in the management of osteoporosis by recommending bone-strengthening exercises, screening individuals for fracture risk, and educating patients on the condition. Osteoblasts respond to mechanical stimulation, and they require high magnitudes of stress in order to strengthen and optimally orient collagen fibers.13 The LIFTMOR randomized control trial demonstrated that high-intensity resistance training increases bone density, cortical thickness, and functional performance in women with osteoporosis.19 In addition to prescribing exercises to enhance the integrity of the bone, physical therapists should also assess and provide interventions for fall risk reduction, ultimately reducing the risk for fracture.

*Articular Cartilage*

 The role of articular cartilage is to protect the underlying subchondral bone from frictional abrasion and high levels of contact pressure. The cartilage is composed predominately of water to increase loading time and a solid matrix of type II collagen, ground substance, and chondrocytes, creating a dense, fluid filled sponge.20 While these structures are the same in men and women, the chondrocytes may play an important role in understanding why there are differing rates of articular cartilage pathology between them. As previously mentioned, aromatase converts testosterone into E2 in the ovaries.6 Schicht et al. found that aromatase mRNA is also located in human chondrocyte cells and is expressed by the articular cartilage.21 Further analysis demonstrated that the chondrocytes are also able to produce estrogens independently of the ovaries.21 When an aromatase inhibitor is applied to the chondrocyte, there is a reduction in estrogen synthesis, increased expression of matrix metalloproteinases, and decreased synthesis of type II collagen.21 Together, this results in reduced integrity and healing ability of the articular cartilage. The relationship between estrogen and the clinical manifestations of articular cartilage pathology is not yet fully understood, and studies on HRT users found a decrease in joint pain but no protective effects against developing osteoarthritis.1

 Osteoarthritis (OA) is the most common articular cartilage pathology and is the leading cause of disability that results in significant knee pain and difficulty with activities of daily living.22 While men tend to develop OA at an earlier age than women, women are 1.84 times more likely to develop OA after 50 years of age, indicating a relationship between OA onset and menopause.22 OA is multifactorial with biochemical and mechanical factors that contribute to its progression and onset. Kumar et al. found that women with OA have greater losses of the collagen matrix in the lateral and patellofemoral compartments compared to men.22 Women with OA also lose patellar cartilage at an annual rate of 3.3% compared to 1.4% for men with OA which correlates with observed higher rates of patellofemoral OA in women.1,22 From a mechanical perspective, gait analysis indicates that middle-aged women with OA have a lower second peak knee adduction moment than men.22 Thus, strategies to reduce these forces, such as recommending walking poles or teaching a medial thrust gait pattern, may not be as effective.

 While the research on the specific biochemical and mechanical factors that contribute to sex differences in OA is ongoing, there is evidence in outcome differences that clinicians should be aware of and work to address. Physical therapy is recommended as “first-line” treatment to reduce pain and improve function in people with knee OA, and women are three times more likely to seek physical therapy services treatment.23,24 Unfortunately, women who undergo total knee arthroplasty (TKA) tend to have worse outcomes than their male counterparts. Wolf reports that after adjusting for preoperative functional limitations and comorbidities, women demonstrated poorer functional levels, a higher dependence on gait aids, and higher pain levels up to five years post-surgery.1 Some contributing factors to these poorer outcomes include the delaying of surgery until a more advanced stage of the disease is reached and higher levels of pre-operative pain. More recently, Clement et al. found no differences in function based on WOMAC scores between men and women undergoing TKA but did find higher levels of dissatisfaction with pain relief.25 The authors attribute these differences to women having higher rates of pain catastrophization which is also associated with persistent knee pain after TKA.25 In addition to providing evidence-based interventions to address biomechanical impairments, mitigating contact pressure, and addressing malalignments, physical therapists should be aware of these differences and contributing factors to pain outcomes and tailor their interventions accordingly.

*Fibrocartilage*

 The structure and function of fibrocartilage is similar to that of articular cartilage in that it decreases joint contact pressure, but its higher proportion of type II collagen fibers and lower proportions of glycosaminoglycans (GAG) and water make it a stiffer and less permeable tissue.26 The meniscus is primarily fibrocartilage and has a secondary function of providing additional joint stability by increasing congruency.26 Meniscal tissues are located in the knee, temporomandibular joint (TMJ), sternoclavicular joints, vertebral facet joints, and the pubic symphysis.26 While the research on the effects of sex hormones on fibrocartilage is limited, there is evidence to suggest that relaxin and E2 both play a role in the repair of the fibrocartilaginous matrix.

Relaxin is a polypeptide hormone that mediates matrix turnover, resulting in a loss of collagen and GAGs from fibrocartilaginous tissues like the pubic symphysis.27 This serves a useful role during pregnancy and birth, when relaxin concentrations increase to allow for the pelvis to accommodate the growing fetus. Unfortunately, women of childbearing age are twice as likely as men to suffer from temporomandibular joint disorders (TMD) which are characterized by the degradation of the fibrocartilaginous disk between the mandibular condyle and glenoid fossa.28,29 While the etiology of TMD is not fully understood, there does appear to be sex-hormone related mechanisms to resulting in increased tissue degradation. It appears that E2 potentiates relaxin in the pubic symphysis and other synovial joints like the TMJ, enhancing the degradation of fibrocartilage through the loss of GAGs and collagen.27 Park et al. administered estrogen and progesterone to ovariectomized mice to mimic concentrations similar to the human reproductive cycle.29 E2 administration resulted in the loss of type II collagen and GAGs and a higher level of expression of metalloproteinases.29 These degradative changes occurred in the TMJ, but had no impact on the knee meniscus, so tissue changes may be location-dependent.27,29 These insights are from animal models, so they may not be applicable to humans. However, Park et al. did report that elevated serum levels of E2 in men and women were positively correlated with TMD symptom severity.29

 TMD presents with pain and limited jaw range of motion that negatively impacts a person’s ability to eat and speak and is often chronic in nature.29 Since the disk functions as a shock absorber between the condyle and fossa, the degradation of the disk increases the contact pressure and causes orofacial discomfort of either the muscles or joint. A recent systematic review and meta-analysis indicates positive effects of manual therapy and exercise interventions to reduce pain and improve jaw motion.30 There is a strong positive correlation between TMD, neck pain, and headaches, so it can be difficult for physical therapists to discern which structures are the source of the patient’s symptoms. Fortunately, there is evidence to suggest that if a patient presents with both TMD and neck pain that cervical spine mobilizations can reduce TMD pain and improve jaw range of motion.30 While physical therapy treatment can be helpful to address the biomechanical contributions to TMD, physical therapists should also be aware that women with TMD are three times more likely to have disk perforations than men.28 This may potentially be the result of hormonal influences promoting the degradation of the fibrocartilage. If a patient is not improving with therapy, referral to an oral surgeon for repair of the disc perforation may be warranted to stop the progression of TMD to OA of the jaw.

*Tendon and Ligament*

 Cycling E2 concentrations during the different phases of the menstrual cycle impact the biomechanical properties of tendon and ligament. These mechanical properties influence their stiffness and are determined by cross-sectional area, collagen fiber orientation, and cross-linkage.6 Stiffer tendons improve performance via efficient force transmission from muscle to bone, but tendons that are too stiff can lead to muscle strains.6 Circulating E2 concentrations have a negative correlation with tendon and ligament stiffness.31 This is because E2 exposure inhibits lysyl oxidase, which is the enzyme that facilitates collagen cross-linkage.31 In addition, type I and II collagen appear to be more susceptible to biomechanical changes from E2 exposure than type III collagen.31 These differences may account for the wide variation in presentation of tendon and ligament impairments between men and women at different sites and relative injury risk.

 Pre-menopausal women are at an 8-time increased risk for anterior cruciate ligament (ACL) injuries and have a decreased risk of achilles tendinopathies compared to post-menopausal women and males. These different risk factors are due to the presence of E2 at the tendon, ligament and musculotendinous junction. Males tend to have stiffer and stronger patellar tendon fascicles at the musculotendinous junction and greater cross-sectional area.31 This allows the tendon to be able to withstand greater ultimate stress before failure. Women do not have this benefit and have higher levels of type III collagen in the patellar tendon which is more elastic, decreasing the ultimate stress and strain at failure, placing the ACL at risk and contributing to joint hypermobility.31 At other sites, the reduced stiffness from E2 exposure is a benefit and decreases the risk of muscle strain injuries. Women who have lower circulating levels of E2 such as those who use COC or are post-menopausal are more likely to develop achilles tendinopathy, have greater muscle damage, and are more likely to experience delayed-onset muscle soreness due to the increased tendon stiffness and tensile loads at the musculotendinous junction.31 Meanwhile, athletes who use COCs have reduced fluctuations in knee joint laxity across the menstrual cycle and decreased anterior tibial translation, reducing the risk of ACL injury.9,31 Thus, COC use can be helpful in preventing ligament injuries especially in athletes who in engage in higher-risk activities, but could also increase the risk for developing tendinopathies.

 Physical therapists must keep these sex differences in mind when developing rehabilitation plans for women with tendon and ligamentous injuries and consider hormone status when developing a differential diagnosis. Since physiologic warming increases tendon stiffness, incorporating ample dynamic warm-up before exercise is paramount particularly for post-menopausal women who are using HRT and post-pubertal women who do not use COC to protect the ligaments before high-impact loading or when recovering from tendon damage. A randomized control trial of adolescent female soccer players found that completing a 15-minute neuromuscular warm-up twice per week significantly reduced the risk of ACL injury.32 Current rehabilitation strategies for tendinopathies focus on high volume loading to increase cross-sectional area and promote parallel fiber orientation. Consequently, women do not respond to high-volume eccentric loading as well as males do. Knobloch et al. found that men with achilles tendinopathy who completed 12 week of eccentric training had greater improvements on the VISA-A and the Foot and Ankle Outcome Score than women.33 Women are more likely to have shoulder pathologies, and those who undergo rotator cuff repair tend to have worse range of motion and strength pre-operatively than men.34 These negative factors remain post-operatively with worse participation and disability limitations and lower satisfaction at 6 months.34 This trend of higher rates of injury and worse outcomes is also observed in ACL repair. In a multi-center case control study, women had significantly poorer pain and functional outcomes across measures.35 It is critical that therapists are aware of these outcome differences and address impairment, activity, and participation-level factors that sustain these discrepancies and target their prevention efforts on those who are at highest risk of injury.

*Muscle*

E2 has anabolic properties that influences the growth of myoblast cells and has a role in regulating inflammatory processes involved with healing and growth.36 Generally, women have smaller muscle CSA that declines over time, peaking around the age of 35.37 Women who use HRT have demonstrated an attenuation or reversal of this age related decline in lean muscle mass and, and fewer biomarkers of inflammation post-exercise.36 In animal models, E2 supplementation improves muscle twitch characteristics, force development and strength, reverses declining muscle CSA, and heals injured muscle fibers.36 E2 also appears to regulate the satellite cells responsible for repairing damaged myofibrils by inhibiting the stimulation of cytokines and growth factors.37 However, there does not appear to be a direct relationship of muscle force, velocity, or power and circulating E2 levels across different phases of the menstrual cycle.38 Studies on COC use and muscle composition have found that formulations with higher levels of progesterone inhibited muscle protein synthesis.6 Clearly this is an area in need of more investigation to understand how sex hormones impacts human muscle tissue.

 Sarcopenia is a syndrome characterized by a loss of muscle mass, strength, and function with aging.39 While sarcopenia impacts both sexes, it is more prevalent in women.39 With age, the muscle CSA decreases and the composition of fibers favors type I over type II fibers resulting in a loss of strength and power.37 Sex differences in histopathology may contribute to the higher prevalence in women. Women have more dramatic and progressive type IIa muscle fiber atrophy than men who have more generalized whole-limb atrophy.40 Other differences in prevalence could be due to differences in common risk factors such as having a sedentary lifestyle, age-related declines in hormones, decreased protein intake and synthesis and decreased motor unit remodeling by satellite cells.39

 Physical therapists routinely manage the non-pharmacological assessment and treatment of sarcopenia by evaluating muscle strength and gait speed. Progressive resistance training and safely increasing physical activity levels are the cornerstone of sarcopenia treatment. Strength training not only increases muscle strength, mass, and physical functioning, it can be particularly beneficial for women by increasing the ratio of type II to type I fibers.39 While there are no reported sex differences in response to resistance training for older adults with sarcopenia, women may benefit from starting resistance training programs earlier to prevent the preferential loss of type II fibers.

*Skin*

 The skin protects internal structures and facilitates joint motion. With age, the epidermis and dermis has reduced cell proliferation and turnover rates, and reduced vascularity result in an altered collagen structure.41 This structural change results in the loss of elasticity, wrinkling, thinning, and susceptibility to injury. The dermis contains hormone receptors and is able to locally synthesize estrogens from cholesterol for local use.41 With menopause, the ability to produce estrogen locally is advantageous for protection as systemic concentrations decline. E2 has been shown to be protective against mitochondrial aging and clinical trials of HRT showed positive effects on collagen content, elasticity, and fragility in post-menopausal women.41 Thus, understanding the role of sex hormones in skin healing is critical for developing targeted therapies to treat wounds.

 The incidence of diabetic wounds has grown with diabetes globally. Having diabetes increases the risk of developing a foot ulcer by 25% and dramatically increases the risk of amputation.42 In post-menopausal women with diabetic foot ulcers, healing can be delayed by lower E2 gene regulation resulting in fewer cytokines, growth factors, extracellular matrix turnover rates and more oxidative stress.43 Nevertheless, a meta-analysis identified that male, not female, gender was an independent risk factor for developing recurrent foot ulcerations.44 Women may be at a biomechanical advantage for preventing diabetic ulcers due to increased subtalar and first metatarsal joint mobility and lower foot pressures.45 Clearly, hormones may not provide a full understanding of sex and gender differences of disease severity and risks. Other factors like health care utilization and lifestyle choices may have more meaningful impact than biological factors.

While physical therapists do perform wound care evaluation and treatment, it would not be within their scope of practice to administer pharmaceutical interventions such as hormonal therapies. Treatments performed by a physical therapist may include debridement and drainage, antimicrobial dressing application, and recommendations for pressure-relieving modalities.46 Exercise interventions are often recommended to improve microvascular circulation, balance impairments, and biomechanical factors such as reduced range of motion and strength. Physical therapists also provide education to help patients manage their wound risk factors.

*Conclusion*

 Understanding sex differences in the structure, function, and healing ability of musculoskeletal tissues is critical in order to provide evidence-based, high-quality care to all patients. Sex steroid hormones, particularly E2, can influence the structure and healing ability of these tissues by regulating gene expression of reparative cells, inhibiting enzymes, and influencing cellular turnover rates. The changes in hormonal concentration across the lifespan may account for the changed risk of developing conditions like osteoporosis, tendinopathies, and osteoarthritis correspond with menopause. Therapists need to understand how hormonal therapeutics impacts the physical therapy plan of care. Despite having a higher prevalence of certain conditions such as shoulder pathologies, ACL tears, and TMD, women consistently have worse functional outcomes. By understanding these differences, physical therapists can implement their interventions more effectively.



**Figure 1:** This is a graphical representation of the relative fluctuations in hormonal concentrations during (A) a normal menstrual cycle, (B) taking a COC, and (C) before and after menopause. Image reprinted from Chidi-Ogbulu N and Baar K, 2018.6

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