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Review Article

Gender-specific diseases in Orthopedics: Etiopathogenesis and clinical perspectives

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Abstract

Many orthopedic disorders exhibit pronounced sex- and gender-based differences in prevalence, pathophysiology, clinical presentation, and outcomes. These differences stem from complex interactions among hormonal milieu, anatomical and biomechanical variations, genetic and immunological factors, and lifestyle/environmental modifiers. This review synthesizes current evidence on major gender-specific orthopedic diseases—osteoporosis, osteoarthritis, anterior cruciate ligament injury, hip fractures, and inflammatory arthropathies—highlighting the etiopathogenesis behind their sexual dimorphism and discussing implications for prevention, diagnosis, and therapy.

Keywords: Sex-based variations, Orthopedic diseases, Osteoporosis, Osteoarthritis, ACL injury, Hormonal modulation

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1. Introduction

Musculoskeletal health is influenced significantly by biological sex (chromosomal, hormonal, anatomical) and gender (social, behavioral) factors. Numerous orthopedic diseases show a marked sex bias: for example, osteoporosis and fragility fractures are far more common in postmenopausal women; autoimmune inflammatory arthropathies such as rheumatoid arthritis display strong female predominance; conversely, certain degenerative conditions may present differently in men. These gender-specific differences are not entirely explained by environmental or sociocultural factors; underlying mechanisms include hormonal regulation of bone and connective tissue metabolism, structural and biomechanical differences in bones, joints, ligaments and muscles, and genetic/immunological variation between sexes.[1–7]

Estrogens, progesterone, testosterone, and other gonadal hormones play pivotal roles beyond reproduction, influencing bone turnover, cartilage homeostasis, ligament laxity, and immune function. Anatomical variations—pelvic width, Q-angle, intercondylar notch size, cortical thickness—affect mechanical loading and injury risk. Genetic factors including sex chromosome differences, gene expression variation (including X-chromosome genes, estrogen receptor polymorphisms), and immune regulatory pathways are increasingly recognized as contributing to sex-specific disease susceptibility.[2,4,7]

This review aims to elaborate on major orthopedic diseases with sex/gender specificity: their epidemiology, etiopathogenesis, and clinical implications, drawing on recent human and molecular research, and to integrate these findings into recommendations for gender-sensitive orthopedic care.

2. Osteoporosis

2.1. Epidemiology

Osteoporosis is characterized by reduced bone mass and deterioration of bone tissue microarchitecture, leading to increased risk of fractures. Women are disproportionately affected, especially after menopause. Approximately one in three women over age 50 will experience an osteoporotic fracture compared to one in five men.[8] Women tend to develop fragility fractures earlier and have higher cumulative

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lifetime risk. Although men have lower fracture incidence, their outcomes (e.g. mortality, functional decline) are often worse.[9]

2.2. Etiopathogenesis

2.2.1. Hormonal decline

The abrupt decline in estrogen at menopause drastically increases osteoclastic activity, reduces suppression of bone resorption, and leads to rapid loss of trabecular bone.[4,10] Estrogen also modulates cytokines (IL-1, IL-6, TNF-α) that drive bone resorption.[4]

2.2.2. Sex differences in bone geometry and peak bone mass

Women typically achieve lower peak bone mass and have narrower bones, thinner cortices, and less favorable cross-sectional geometry, resulting in lower mechanical resistance to bending and torsion. Men display more periosteal apposition with age, which partly compensates cortical thinning; women less so.[8,11]

2.2.3. Genetic and molecular influences

Polymorphisms in estrogen receptors (ERα, ERβ), vitamin D receptor, collagen type-1, and genes regulating bone remodeling (e.g., RANK/RANKL/OPG) show sex-based effects. Epigenetic modulation further contributes.

2.2.4. Lifestyle and environmental factors

Differences in diet (calcium, vitamin D), physical activity (especially weight-bearing and resistance training), body composition (lean mass vs fat), exposure to risk factors such as smoking and medications (glucocorticoids) contribute, often with sex-biased prevalence.

2.3. Clinical Implications

2.3.1. Screening

Earlier and more frequent bone mineral density measurement (DXA) in women, especially around menopause; men with risk factors assessed proactively.

2.3.2. Preventive strategies

Lifestyle modifications, adequate calcium and vitamin D, exercise regimens emphasizing strength and balance.

2.3.3. Pharmacotherapy

Antiresorptive agents (bisphosphonates, denosumab), anabolic agents (teriparatide) are effective; hormone replacement therapy may confer benefits in women but needs careful risk-benefit evaluation.

3. Osteoarthritis (OA)

3.1. Epidemiology and gender differences

OA is a degenerative joint disease marked by progressive cartilage degradation, synovial inflammation, subchondral bone changes, and pain. After age 50, women show much higher incidence, particularly of knee, hand, and some hip OA; they also report more pain and disability, and faster radiographic progression.[1,7,12]

3.2. Etiopathogenesis

3.2.1. Estrogen deficiency and aging

Loss of estrogen post-menopause is associated with increased chondrocyte senescence, decreased ECM (extracellular matrix) synthesis, increased expression of catabolic enzymes (MMPs, ADAMTS) and pro-inflammatory cytokines. Transcriptomic studies reveal that estrogen deficiency accelerates molecular pathways leading to cartilage breakdown, including overexpression of MMP-13 and inflammatory interleukins (IL-1β, IL-6, etc.).[7,13]

3.2.2. Estrogen receptors and polymorphisms

Both ERα and ERβ are expressed in articular cartilage; variation in their expression or gene polymorphisms correlates with OA risk and progression. Endogenous & exogenous estrogen (e.g. through HRT) also appear protective in several epidemiologic studies.[1,14]

3.2.3. Biomechanical and anatomical influences

Women often have greater valgus knee alignment, higher Q-angle, less muscle mass and strength around joints, altered gait biomechanics, greater joint laxity; all increase mechanical stress on cartilage surfaces.

3.2.4. Inflammation and immunomodulation

Estrogen exerts anti-inflammatory effects; deficiency predisposes to increased synovial inflammation. Emerging research implicates immune cell infiltration, chemokine pathways, senescence-associated secretory phenotype in joint tissues more pronounced in females.[7]

3.3. Clinical implications

1. Consider hormone status (menopause, HRT) when evaluating OA risk.
2. **Interventions:** weight control, strengthening of periarticular muscles (quadriceps, hip abductors), joint alignment correction, neuromuscular training.
3. **Potential therapeutic targets:** modulating estrogen receptors, targeting catabolic enzymes, anti-inflammatory biologics, exploring senolytics.

4. Anterior Cruciate Ligament (ACL) Injuries

4.1. Epidemiology

Female athletes are reported to have 2-8 times higher risk of non-contact ACL injury than male athletes in similar activities. Young female athletes in sports like soccer, basketball, etc. are especially vulnerable.[15]

4.2. Etiopathogenesis

4.2.1. Hormonal fluctuations

Relaxin, estrogen, progesterone levels vary across menstrual cycle; studies show peak relaxin levels (days ~21-24) associate with upregulated collagen degradation and lowered collagen synthesis in ACL tissue. Low levels of estrogen and progesterone in certain phases affect ligament strength. Oral contraceptive use appears associated with reduced incidence of ACL injury in some cohorts.

4.2.2. Anatomical and biomechanical risk factors

Females tend to have narrower intercondylar notch, smaller ACL cross-sectional area, increased posterior tibial slope, wider pelvis and higher Q-angle; weaker hamstrings relative to quadriceps, lower hip and core strength; landing mechanics that favor valgus collapse and lower knee flexion.[15]

4.2.3. Joint laxity and connective tissue biology

Estrogen and relaxin modulate collagen turnover; relaxin receptors in female ACL bind relaxin and increase expression of collagen-degrading receptors when pretreated with estrogen. Reduced baseline sex hormone levels (estrogen, progesterone, testosterone) have been found in females with ACL rupture compared to controls.[16]

4.3. Clinical implications

1. **Preventive programmes:** neuromuscular training, plyometrics, balance training, hip/hamstring strengthening.
2. Consider risk modulation via hormonal methods (e.g. contraceptives) though evidence is not yet conclusive.
3. Surgical considerations: graft size, extra-articular augmentation (e.g. lateral tenodesis) in female athletes under age 21 to reduce failure rates.[15]
4. Timing of training and competition phases relative to menstrual cycle might be considered in elite athletes.

5. Hip Fractures and Femoral Neck Fragility

5.1. Epidemiology

Hip fractures due to low trauma are much more common in elderly women, especially post-menopausal. The incidence rises sharply with advancing age; women carry the higher absolute risk burden, though men often suffer worse outcomes.

5.2. Etiopathogenesis

Loss of trabecular and cortical bone due to estrogen deficiency; increased cortical porosity, thinning of cortical thickness, reduced cross-sectional area increases susceptibility to fracture under load.[8]

Poor muscle mass, reduced hip abductor strength, decreased mobility and higher fall risk in older women compound the skeletal fragility.

Comorbidities such as vitamin D deficiency, endocrine disorders, renal disease are more prevalent or more impactful in women.

5.3. Clinical implications

1. Screening and preventive protocols: DXA, fall prevention, strength and balance training.
2. Consider pharmacologic therapy, possible surgical intervention earlier.

6. Inflammatory Arthropathies (Rheumatoid Arthritis, SLE, etc.)

6.1. Epidemiology

Diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are significantly more common in women. RA female-to-male ratio is ~2-3:1; SLE even higher. Female patients often present at younger age, with more frequent extra-articular involvement, higher disease activity, and more pronounced functional impairment.[2,17,18]

6.2. Etiopathogenesis

6.2.1. Immune regulation & hormonal effects

Estrogens modulate immune cell activity, promoting B-cell activity, autoantibody production. Progesterone and testosterone tend to suppress some inflammatory pathways. Hormonal fluctuations (pregnancy, postpartum, menopause) often correlate with disease activity changes.

6.2.2. Genetic factors

HLA alleles show sex associations in RA; familial RA shows differences in age of onset and genetic background in women versus men. Recent transcriptomic and Mendelian randomization studies identify gender-differential gene expression in RA (e.g. higher immune cell infiltration, key differentially expressed genes (DEGs) in women).[2,5]

6.2.3. Sex differences in presentation and course

Women tend to report more pain, fatigue, have more joint swelling, and worse physical function; they may also respond differently to treatment, and achieve remission less often or more slowly.[19]

6.3. Clinical implications

1. **Gender-aware diagnosis:** high index of suspicion in women, especially younger women with joint symptoms.
2. Early aggressive therapy may be more beneficial to prevent irreversible joint damage in female patients.
3. Consider hormonal status, co-morbidities, and differences in pharmacodynamics in treatment plans; ensure adequate representation of both sexes in clinical trials.

7. Integration: Common Themes and Mechanisms

From the above disease-specific discussions, several recurring mechanisms underpin sexual dimorphism in orthopedic disease:

1. **Hormonal modulation:** Estrogen, progesterone, testosterone, relaxin — influencing bone, cartilage, ligament, immune cells.
2. **Anatomical and biomechanical differences:** Bone geometry, joint alignment, muscle strength, Q-angle, ligament size.
3. **Genetic and molecular differences:** Sex chromosome effects, polymorphisms in receptors (ERα, ERβ), immune genes (HLA, cytokine regulation), transcriptomic differences.
4. **Effects of aging and hormone lifespan transitions:** Puberty, pregnancy, menopause (in women), and in men, andropause or hypogonadism.
5. **Lifestyle, environmental exposures, and comorbidities:** Physical activity, diet, exposure to risk (smoking, medications), fall risk, social determinants.[20]

8. Adolescent Idiopathic Scoliosis (AIS)

8.1. Epidemiology

AIS is the most common spinal deformity in children and adolescents, affecting 2–3% of school-aged children. Marked sexual dimorphism exists: while mild curves occur with similar frequency in both sexes, progressive curves requiring intervention are up to 8–10 times more common in females.[21]

8.2. Etiopathogenesis

8.2.1. Hormonal influences

Estrogen and melatonin signaling abnormalities have been implicated. Reduced melatonin receptor function and altered estrogen receptor expression may contribute to curve progression.[22]

8.2.2. Growth and skeletal maturity differences

Females typically undergo earlier pubertal growth spurts, with rapid skeletal growth outpacing spinal stability, predisposing to curve progression.

8.2.3. Genetic factors

Genome-wide association studies (GWAS) have identified susceptibility loci (e.g., LBX1, GPR126), with stronger associations in females.

8.2.4. Neuromuscular and biomechanical contributions

Differences in proprioception, muscle balance, and spinal biomechanics between sexes may exacerbate curve progression.

8.2. Clinical implications

1. **Screening:** Early detection in adolescent girls is crucial.
2. **Bracing:** More frequently required in females; compliance and timing relative to menarche are critical.
3. **Surgical considerations:** Curve type and correction strategies may differ.

9. Stress Fractures in Female Athletes

9.1. Epidemiology

Stress fractures are common overuse injuries in athletes and military recruits. Female athletes, particularly in endurance sports, exhibit higher rates than males, often linked to the female athlete triad/RED-S (Relative Energy Deficiency in Sport).

9.2. Etiopathogenesis

1. **Low energy availability:** Inadequate caloric intake relative to expenditure leads to impaired bone remodeling.
2. **Menstrual dysfunction:** Hypoestrogenism from amenorrhea reduces bone mineral density and increases fracture risk.
3. **Low bone mineral density:** Suboptimal bone mass and microarchitectural weakness predispose to fatigue failure.
4. **Biomechanical factors:** Differences in lower-limb alignment, muscle strength, and gait mechanics contribute.

9.3. Clinical implications

1. **Prevention:** Adequate nutrition, energy balance, screening for menstrual dysfunction.
2. **Early diagnosis:** MRI is preferred for early stress reaction detection.
3. **Rehabilitation:** Gradual return-to-sport, correcting biomechanical risk factors, hormonal restoration if necessary.

10. Discussion

Recent advances in orthopaedics reinforce that gender dimorphism in musculoskeletal disease is more than just hormone levels or simple anatomical differences. Emerging research highlights nuanced interactions among neuromuscular fatigue, tissue mechanical properties, recovery trajectories, and sex-based control strategies. These offer deeper insights into why incidence, presentation, and outcomes differ between males and females — and suggest novel intervention and research targets.

Firstly, neuromuscular fatigue has been shown to produce sex-distinct biomechanical alterations that may heighten injury risk in females. A 2025 systematic review and meta-analysis found that after neuromuscular fatigue, males exhibited a significant increase in knee flexion at initial contact, whereas females did not; however, both sexes showed elevated hip external rotation and ankle loads.

These mechanistic changes are likely to impact ligamentous strain (especially on the ACL) and may account for some of the higher non-contact injury rates among female athletes. Similarly, a study using hip extensor and knee flexor fatigue protocols found that fatigue disproportionately reduces hip/knee flexion in females compared to males during landing tasks and modifies muscle activation patterns, with implications for neuromuscular control strategies.

Secondly, there is increasing evidence on sex differences in ligament properties mediated by hormones. A systematic review and meta-analysis of how sex hormones (notably 17β-estradiol and relaxin) affect ligament mechanical and cellular properties shows that hormonal fluctuations (in menstrual cycle, pregnancy, contraceptive use, menopause) alter collagen synthesis (types I & III), fibroblast behavior, and possibly stress tolerance. Although knee laxity (objective translation) did not always change in some studies, these molecular and microstructural changes likely compromise ligament strength and contribute to injury susceptibility.

Third, neuromuscular activation patterns during dynamic tasks differ by sex even in healthy populations, which has downstream effects on stability and injury risk. For example, a systematic review of EMG studies comparing knee stabilisers in males and females found that females sometimes exhibit greater activation in quadriceps (vastus medialis/lateralis) during certain tasks, but lower activation in hamstring or posterior chain muscles; the inconsistent findings emphasize variability but point to a need for better power, task standardization, and normalization of EMG metrics.[22]

Fourth, outcome and recovery differences after surgical or injury events also show gendered patterns. One study (2025) comparing physical and psychological recovery following ACL reconstruction reported that women had lower subjective knee function, lower psychological readiness for return-to-sport, and lower strength recovery compared to men at multiple time points (6, 12, 24 months) post-surgery. Another study one year post ACL reconstruction found women had significantly greater deficits in quadriceps strength compared to men, though hamstring strength deficits were similar.[23]

Finally, in vivo dynamics of knee kinematics and ACL elongation reinforce sex-based differences under physiologic loading. In collegiate athletes performing high-impact activities (running, drop jump, hopping), women showed significantly greater ACL elongation and altered knee adduction/abduction kinematics compared to men, even among uninjured individuals. These findings suggest that screening and rehabilitation may need to account for sex-specific baseline mechanics, not just pathology.[23]

11. Conclusion

Gender-specific differences in orthopedic diseases stem from a complex interplay of hormonal, anatomical, genetic, biomechanical, and social factors. Recognizing and incorporating these differences into clinical practice can enhance preventive strategies, improve diagnostic accuracy, and optimize therapeutic outcomes. Future research must prioritize sex-stratified study designs and integrate mechanistic, molecular, and biomechanical data to enable personalized musculoskeletal care.

12. Future Directions

1. More longitudinal human studies with hormone assays, imaging, molecular biomarkers, stratified by sex.
2. Clinical trials of preventive strategies tailored by sex (e.g. hormonal interventions, neuromuscular training, timing of activity).
3. Development of therapies targeting molecular pathways that differ by sex (e.g., modulators of estrogen receptor signalling, senescence pathways in cartilage).
4. Greater inclusion and disaggregation by sex in research, ensuring both male and female subjects are adequately represented.

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