Review

Knee Osteoarthritis, Hormonal Decline, and Chronic Inflammation in Midlife Women: Hormone Therapy as a Modulator of the Osteoarthritis Disease Environment: An Orthopaedic and Integrative Clinical Perspective

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Knee Osteoarthritis, Hormonal Decline, and Chronic Inflammation in Midlife Women: Hormone Therapy as a Modulator of the Osteoarthritis Disease Environment: An Orthopaedic and Integrative Clinical Perspective

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Abstract

Background: Knee osteoarthritis (OA) is traditionally framed as a mechanical "wear-and-tear" disorder. Contemporary evidence supports OA as a whole-joint, immunometabolic and neurosensory disease in which low-grade chronic inflammation modulates tissue homeostasis and pain. In midlife women, the menopause transition coincides with abrupt endocrine changes that plausibly amplify inflammatory tone, alter neuromuscular function, and increase pain sensitisation—often with symptoms disproportionate to imaging. **Objective:** To synthesise the biological rationale and clinical evidence linking menopausal hormonal decline with OA-relevant inflammatory and neuromuscular mechanisms, and to propose a collaborative orthopaedic model integrating menopause health expertise. **Methods:** Narrative review of mechanistic, epidemiologic, and clinical trial data on OA inflammation, menopause-related musculoskeletal symptoms, and hormone therapy effects on pain/function and musculoskeletal resilience**.** Evidence is interpreted with attention to outcome type (symptoms vs structural progression), confounding in observational studies, and timing/continuity considerations. **Key Findings:** (1) OA pain and disability correlate imperfectly with radiographic severity, consistent with synovitis, adipose-derived mediators, subchondral remodelling, and peripheral/central sensitisation. (2) Perimenopause is associated with increased prevalence of musculoskeletal pain, suggesting a biological inflection period rather than linear age-related decline. (3) Oestrogen decline plausibly shifts immune signalling toward pro-inflammatory pathways (e.g., IL-6/TNF-α/NF-κB), while progesterone and androgen changes may influence sleep quality, recovery capacity, muscle strength, and neuromuscular control—factors strongly linked to knee OA outcomes. (4) Menopausal hormone therapy (when appropriately indicated and supervised) may reduce joint pain in some women and may improve musculoskeletal resilience; however, evidence for disease-modifying structural effects on OA remains limited and confounded. **Clinical Implications:** Orthopaedic care for midlife women with knee OA should include endocrine-aware phenotyping, screening for menopause-transition symptom clusters, and structured referral pathways to women's hormonal health specialists. Optimising the systemic biological environment may enhance the durability of rehabilitation, regenerative strategies, and surgical outcomes. **Conclusion:** Menopause transition biology is a clinically relevant modifier of OA symptom expression and functional decline. Integrating hormonal health expertise into orthopaedic pathways is not scope expansion—it is precision care aligned with modern OA biology.

Keywords: knee osteoarthritis; menopause; perimenopause; chronic low-grade inflammation; pain sensitisation; menopausal hormone therapy; joint preservation; sarcopenia; synovitis; IL-6; TNF-α; NF-κB

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Highlights

- OA is a whole-joint, immunometabolic, and neurosensory disease—not cartilage wear alone.
- Perimenopause appears to be a musculoskeletal inflection period with increased pain prevalence.
- Hormonal decline plausibly amplifies low-grade inflammation and pain sensitisation while impairing neuromuscular resilience.
- Hormone therapy may modulate symptoms and musculoskeletal function in selected women, but structural disease-modifying evidence is limited.
- Orthopaedic care may be optimised with endocrine-aware phenotyping and referral pathways.

Chapter 1

Osteoarthritis, Women, and the Menopause Transition: Why Orthopaedics Must Integrate Biology

Osteoarthritis is not simply a joint problem. It is a systems-level disability problem. Osteoarthritis (OA) is the most prevalent chronic musculoskeletal disease and a major driver of long-term pain, disability, healthcare utilisation, and loss of independence. Its societal burden is amplified by ageing populations, metabolic disease, physical inactivity, and increased life expectancy [1–3].

OA is still commonly framed as an inevitable mechanical consequence of ageing—"wear and tear." The model is intuitive and partly true, but biologically incomplete. In midlife women, this simplification is not harmless: it delays recognition of modifiable systemic contributors that shape symptom severity, recovery capacity, and functional decline.

Knee and hip OA: where disability begins

OA can involve many synovial joints, but knee and hip OA dominate disability because they govern locomotion. When these joints fail, physical activity declines, muscle mass is lost, weight increases, metabolic risk worsens, and mechanical overload escalates. The result is a predictable feedback loop: reduced movement accelerates the very biological and mechanical conditions that worsen OA and drive progression toward joint replacement [1].

OA as a disease of the joint as an organ

Orthopaedic practice repeatedly exposes a paradox inconsistent with a purely mechanical abrasion model:

- Some patients demonstrate severe radiographic degeneration with minimal symptoms.

- Others experience severe pain, stiffness, fatigue, and functional limitation despite modest imaging findings.

If OA pain were simply proportional to cartilage loss, symptoms would map cleanly onto radiographic severity. They do not. This mismatch reflects OA as a disease involving multiple tissues and regulatory systems—synovium, subchondral bone, menisci, ligaments, fat pad, periarticular muscle, and neural pain processing—rather than cartilage alone [4].

Modern research conceptualises OA as a disease of the joint as an organ, involving: articular cartilage, subchondral bone, synovium, menisci, ligaments, infrapatellar fat pad, periarticular muscles, and peripheral/central pain pathways [4]. This joint-organ system is metabolically active, immunologically responsive, and sensitive to systemic signals. Mechanical load matters—but it acts inside a biological environment that can buffer stress or magnify damage.

Chronic low-grade inflammation: the silent amplifier

OA is increasingly recognised as a condition in which hronic low-grade inflammation amplifies tissue degeneration and pain. Cytokines and inflammatory transcription pathways (e.g., IL-6, TNF-α, NF-κB) influence chondrocyte metabolism, extracellular matrix turnover, synovial activation, subchondral remodelling, and nociceptive sensitisation [5–7]. Clinically, this aligns with a common midlife presentation: pain not limited to joint loading, stiffness at rest, diffuse aching, fatigue, and impaired recovery.

This is not "normal ageing." It is physiology with a shifted inflammatory setpoint.

Menopause transition: a musculoskeletal inflection period

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Perimenopause and menopause are often framed as gynaecological milestones, but they represent a systemic endocrine transition that affects joints, muscle, bone, connective tissue, metabolism, and pain regulation. For years, clinicians observed abrupt escalation of musculoskeletal symptoms in midlife women and dismissed it as inevitable ageing. That dismissal is increasingly untenable.

A 2026 systematic review and meta-analysis (JBJS Open Access; 37 studies; 93,021 women) reported significantly increased risk of muscle and joint pain during perimenopause compared with premenopause (RR ~1.35) [8]. Notably, symptom prevalence did not rise further from perimenopause to postmenopause, consistent with an inflection period rather than a linear age-driven process [8]. However, the review captured symptoms more reliably than orthopaedic diagnoses (OA vs tendinopathy vs bursitis vs sensitisation phenotypes), indicating a major interpretive gap: the symptom burden is documented; the orthopaedic phenotyping remains under-developed [8].

Why women are disproportionately affected

Women represent a majority of OA cases globally and often show faster symptom burden and structural deterioration after midlife [9–12]. Oestrogen receptors exist in cartilage, bone, synovium, and immune cells [13]. High oestrogen states are often associated with anti-inflammatory signalling, while oestrogen decline is linked to shifts toward pro-inflammatory immune tone [13]. This does not imply oestrogen "prevents OA," but it supports a more precise claim: endocrine change modulates the inflammatory and neuromuscular context in which OA symptoms and function evolve.

Why this is an orthopaedic problem (without scope expansion)

Orthopaedics manages the endpoint of musculoskeletal failure: persistent disability, falls, and joint replacement. Ignoring systemic biological drivers does not preserve orthopaedic identity—it limits clinical effectiveness. Recognising hormonal decline as a relevant modifier does not mean orthopaedic surgeons should prescribe hormone therapy. It means orthopaedic pathways must be biologically literate and structurally collaborative.

Aim of this manuscript

This article aims to:

1. Reframe OA as a whole-joint, biologically modulated disease.
2. Highlight the menopause transition as a musculoskeletal inflection period.
3. Summarise biological plausibility and clinical evidence linking hormonal decline with inflammation, pain sensitisation, and functional decline relevant to OA.
4. Justify structured collaboration between orthopaedics and women's hormonal health specialists to improve outcomes.

Mechanical thinking is necessary. It is not sufficient.

Table 1. Evidence Map Linking Menopause-Related Hormonal Decline to Osteoarthritis-Relevant Biological and Clinical Outcomes.

Claim / Link	Outcome	Evidence type	Strength	Main limitations
OA involves synovium/subchondral bone/fat pad + sensitization (joint as organ)	Pain/function more than cartilage loss	Mechanistic + imaging + clinical correlations	High	Heterogeneity of OA phenotypes
Chronic low-grade inflammation (IL-6/TNF-α/NF-κB) amplifies OA pain biology	Pain sensitization, flares, tissue catabolism	Mechanistic + observational	High	Biomarkers not always specific; causality complex

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Perimenopause is associated with increased MSK pain prevalence	Symptoms	Systematic review/meta-analysis	Moderate–High	Diagnostic specificity poor (OA vs non-OA pain)
Estrogen decline plausibly shifts immune tone pro-inflammatory	Biomarkers/pathways	Mechanistic + translational	Moderate	Translating pathway shifts to clinical OA outcomes is indirect
MHT/HRT reduces joint pain in some women	Symptoms	RCT/post-hoc + observational	Moderate	Effect size modest; population selection; not OA-specific
MHT/HRT reduces OA incidence/progression	Structural OA	Observational cohorts	Low–Moderate	Confounding/healthy-user bias; inconsistent measures
Progesterone influences sleep/pain modulation	Sleep quality, pain sensitivity	Mechanistic + clinical associations	Moderate	Indirect OA linkage
Testosterone supports lean mass/strength in women	Strength/body composition	Clinical trials + physiology	Moderate	OA-specific endpoints scarce
Vitamin D repletion improves muscle function/falls risk; pain associations in OA	Function, falls; pain	RCTs mixed + observational	Moderate	Baseline deficiency matters; cartilage effects uncertain

Chapter 2

Chronic Low-Grade Inflammation, Pain Sensitisation, and Joint Degeneration: The Biological Substrate of Osteoarthritis

Osteoarthritis does not behave like an acute injury. It does not arise from a single inflammatory insult that resolves. Instead, it evolves within a persistent, low-grade inflammatory milieu that reshapes tissue behaviour gradually but continuously over time [5–7]. This inflammatory state is qualitatively different from the synovitis of classical inflammatory arthropathies. It is subtler, less overtly destructive, and frequently underestimated. Yet its biological impact is substantial.

From a clinical perspective, this explains a recurring observation in orthopaedic practice: pain at rest, sleep disturbance, diffuse periarticular aching, and impaired recovery capacity often coexist with modest structural change. These features are not well explained by cartilage thinning alone.

Molecular drivers: cytokines and inflammatory signalling pathways

At the molecular level, osteoarthritis is characterised by dysregulated signalling within the joint microenvironment. Key mediators include interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), and the transcription factor nuclear factor kappa B (NF-κB) [6,7]. These molecules influence disease behaviour through several interrelated mechanisms:

- **Chondrocyte catabolism:** Pro-inflammatory cytokines shift chondrocytes from anabolic to catabolic states, increasing expression of matrix metalloproteinases (MMPs) and aggrecanases that degrade extracellular matrix [6].
- **Synovial activation:** Even in so-called "non-inflammatory" OA, histological studies demonstrate synovial hyperplasia, macrophage infiltration, and cytokine production [5,14].
- **Subchondral bone remodelling:** Cytokine-driven alterations in osteoblast and osteoclast activity affect load transmission across the osteochondral unit, modifying mechanotransduction [6,15].

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- **Nociceptor sensitisation:** Cytokines increase peripheral nociceptor excitability and interact with central pain pathways, lowering pain thresholds and prolonging responses [16,17].

These pathways are not linear. They are self-reinforcing. Once established, low-grade inflammatory signalling sustains itself, even if the original mechanical trigger is relatively modest.

The joint is not isolated: systemic inflammation and metabolic interaction

Osteoarthritis is increasingly recognised as both a local joint disease and a systemic inflammatory condition. Circulating mediators influence joint tissues, and joint-derived cytokines may spill into systemic circulation [15]. This bidirectional interaction helps explain the clustering of OA with metabolic conditions such as obesity, insulin resistance, and dyslipidaemia [18]. Adipose tissue functions as an endocrine organ, producing adipokines that modulate cartilage metabolism, synovial activation, and inflammatory tone [18,19].

The infrapatellar fat pad is particularly relevant in knee OA. Rather than serving as passive cushioning, it secretes inflammatory mediators and neuroactive substances capable of influencing both cartilage metabolism and pain perception [20,21]. Importantly, fat pad pathology may correlate with pain severity independently of radiographic damage [20]. This observation reinforces a central concept: pain in OA is not a simple readout of cartilage loss.

Osteoarthritis is frequently described as a cartilage disease, yet periarticular muscle dysfunction is one of the strongest predictors of pain, disability, and progression.

Chronic low-grade inflammation contributes to:

- Loss of muscle mass and strength (sarcopenic tendencies)
- Altered neuromuscular activation and arthrogenic muscle inhibition
- Reduced tendon elasticity and altered ligamentous mechanics

Quadriceps weakness, in particular, is consistently associated with symptom severity and progression in knee OA [22,23]. When dynamic joint stability deteriorates, mechanical stress on articular surfaces increases, amplifying structural vulnerability.

This creates a feedback loop: inflammatory signalling impairs neuromuscular function; impaired neuromuscular control increases joint loading variability; abnormal loading further stimulates inflammatory pathways.

Mechanical and biological drivers are therefore inseparable in clinical reality.

Pain is not proportional to damage: peripheral and central sensitisation

Pain in osteoarthritis reflects both peripheral and central mechanisms. Peripheral nociceptors within synovium, subchondral bone, ligaments, and fat pad are sensitised by inflammatory mediators [16,17]. Repeated nociceptive input alters central pain processing, leading to:

- Lower mechanical and thermal pain thresholds
- Expanded receptive fields
- Persistent pain despite minimal peripheral stimulus

This framework explains why some patients exhibit widespread musculoskeletal pain, sleep disturbance, fatigue, and mood changes alongside localised joint pathology [16,17]. These features overlap with recognised pain sensitisation phenotypes and are particularly prevalent in women.

It is essential to differentiate structural OA from pain-amplification syndromes, yet these states frequently coexist and potentiate one another.

Distinguishing structural OA from menopause-associated musculoskeletal pain

A critical conceptual distinction is required.

Perimenopause is associated with increased prevalence of musculoskeletal pain [8]. However, symptom-based epidemiological data do not reliably differentiate between:

- Radiographic or symptomatic osteoarthritis
- Tendinopathies and enthesopathies
- Bursitis or capsulitis
- Myofascial pain
- Central sensitisation phenotypes

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Failure to separate these entities risks over-attributing all perimenopausal pain to osteoarthritis progression.

The available evidence supports the following:

1. Perimenopause is associated with increased musculoskeletal pain prevalence [8].
2. OA pain severity does not correlate perfectly with radiographic change [16,17].
3. Inflammatory signalling and pain sensitisation contribute substantially to symptom expression [5–7,16].

What remains less definitively established is the degree to which menopause transition accelerates structural OA progression independent of mechanical factors. Observational data suggest associations but confounding and heterogeneity limit causal inference [9–12,31–33].

Clarity here is essential. The argument is not that menopause "causes" osteoarthritis. It is that endocrine transition plausibly amplifies inflammatory and neuromuscular conditions that shape symptom expression and functional decline within pre-existing or incipient joint disease.

The perimenopause inflection revisited: inflammation as a plausible mediator

A 2026 JBJS Open Access systematic review and meta-analysis reported increased risk of musculoskeletal pain during perimenopause, followed by stabilisation in postmenopause [8]. This pattern suggests a transitional biological state rather than linear age-related accumulation.

During perimenopause, fluctuating oestradiol levels influence immune regulation, cytokine expression, connective tissue turnover, and neuromuscular performance [24,34]. These effects may:

- Increase inflammatory tone
- Lower pain thresholds
- Reduce muscle recovery capacity
- Exacerbate existing structural joint vulnerability

The result is a period of heightened symptom expression.

Whether this window also accelerates structural cartilage degeneration remains under investigation. Current evidence supports inflammatory and neuromuscular modulation more strongly than definitive structural disease modification.

Clinical implications: why inflammation-aware orthopaedics matters

Failure to recognise chronic low-grade inflammation as a central substrate of OA has practical consequences:

- Persistent pain despite technically adequate structural interventions
- Suboptimal rehabilitation response
- Variable efficacy of regenerative therapies
- Escalation to surgery without optimisation of biological context

Repeated local intervention within a persistently pro-inflammatory environment may produce diminishing returns.

Understanding inflammation as a core driver reframes the treatment objective. The goal is not solely to correct structure, but to optimise the biological terrain in which structure operates [5–7].

Chronic low-grade inflammation sits at the intersection of immunity, metabolism, connective tissue biology, neuromuscular integrity, and pain processing. These systems are strongly influenced by endocrine signalling [24].

Hormonal decline does not create osteoarthritis de novo. It may, however, shift the inflammatory and neuromuscular setpoint of the musculoskeletal system. Within this altered environment, symptoms intensify, recovery slows, and mechanical vulnerability increases.

The next question is not whether hormones "treat" OA, but whether endocrine optimisation can modify the disease environment in clinically meaningful ways.

That distinction matters.

Chapter 3

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Hormonal Decline as an Inflammatory Amplifier in Osteoarthritis: Biological Rationale, Clinical Signals, and Therapeutic Boundaries

Hormones are systemic regulators of immune tone, tissue metabolism, neuromuscular integrity, and pain processing. Within the musculoskeletal system, endocrine signalling influences cartilage homeostasis, subchondral bone remodelling, muscle mass maintenance, connective tissue elasticity, and nociceptive modulation.

The menopause transition represents a relatively abrupt endocrine shift occurring over a compressed biological timeframe. From an orthopaedic perspective, this transition may function as a stress test for joint homeostasis: tissues previously compensated under stable endocrine conditions are exposed to altered inflammatory and anabolic signalling.

The critical distinction must be maintained: hormonal decline does not initiate osteoarthritis de novo. It may, however, amplify inflammatory tone, impair neuromuscular resilience, and modulate symptom expression within existing or incipient joint disease.

1. Oestrogens: Immune Modulation and Joint Tissue Signalling

Oestrogen receptors (ERα and ERβ) are expressed in cartilage, subchondral bone, synovium, skeletal muscle, and immune cells [24–26]. Oestrogen signalling exerts complex immunomodulatory effects that are dose-dependent and context-specific.

At physiological concentrations, oestrogens are generally associated with:

- Downregulation of NF-κB activation
- Reduction of IL-6 and TNF-α production
- Modulation of macrophage phenotype toward less pro-inflammatory states
- Influence on osteoclast–osteoblast coupling and bone remodelling dynamics [24,27]

Loss or fluctuation of oestrogen signalling during perimenopause may shift immune tone toward a more pro-inflammatory baseline. This shift does not equate to inflammatory arthritis. It represents a change in inflammatory setpoint.

Effects on cartilage and subchondral bone

Chondrocytes express oestrogen receptors and respond to oestrogenic signalling in vitro and in animal models. Experimental oestrogen deficiency has been associated with:

- Increased cartilage matrix degradation
- Altered chondrocyte apoptosis
- Disrupted extracellular matrix turnover [28,29]

In subchondral bone, oestrogen decline modifies remodelling kinetics and may alter stiffness of the osteochondral unit, influencing load transmission [27,30].

These mechanistic observations support biological plausibility. However, translational extrapolation to human structural OA progression must be cautious.

Clinical evidence: symptoms versus structure

Epidemiologically, osteoarthritis prevalence and symptom burden increase in women after midlife, with sex differences widening post-menopause [9–12]. Observational studies have reported associations between current oestrogen use and lower prevalence of radiographic knee or hip OA [31–33].

However:

- Many of these studies are observational.
- Confounding (body mass index, activity level, socioeconomic status, healthcare access) is difficult to eliminate.
- Healthy-user bias may inflate protective associations.

Randomised data provide more robust insight into symptom outcomes. Post hoc analyses of large trials, including the Women's Health Initiative, demonstrated modest but statistically significant reductions in joint pain frequency among women receiving oestrogen compared with placebo [35].

Importantly:

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- Effect sizes were modest.
- Structural disease modification was not the primary endpoint.
- Benefit appeared more pronounced in symptomatic subgroups.

Current evidence therefore supports a moderate level of confidence that oestrogen therapy may reduce joint pain in selected women. Evidence supporting prevention or reversal of structural OA progression remains limited and inconsistent [31–33].

Precision here strengthens credibility.

2. Progesterone: Pain Modulation, Sleep, and Neuromuscular Recovery

Progesterone is frequently confined to reproductive discourse. This obscures its broader neuroendocrine and immunomodulatory roles.

Progesterone receptors are present in the central nervous system, and progesterone exhibits anti-inflammatory and neuroprotective properties [36,37].

Experimental data suggest progesterone may:

- Inhibit pro-inflammatory cytokine production
- Modulate microglial activation
- Influence nociceptive signalling pathways[36–38]

Clinically, progesterone decline during perimenopause is associated with sleep disturbance, increased pain sensitivity, and reduced recovery capacity [38–40]. Sleep disruption independently elevates inflammatory mediators and amplifies pain perception [41].

While direct evidence linking progesterone replacement to OA structural outcomes is lacking, its influence on sleep quality, central pain processing, and neuromuscular recovery provides a plausible indirect pathway through which symptom severity may be modulated.

The strength of evidence here is moderate for sleep and pain modulation, low for OA-specific structural endpoints.

3. Testosterone: Female Musculoskeletal Anabolism and Joint Stability

Testosterone plays a physiological role in women, contributing to maintenance of lean muscle mass, strength, and neuromuscular coordination [42–44]. Testosterone receptors are expressed in skeletal muscle and connective tissue, and physiological androgen levels support anabolic signalling.

Declining androgen levels in midlife women are associated with:

- Reduced lean body mass
- Decreased muscle strength and power
- Impaired dynamic joint stability

Quadriceps weakness is a recognised predictor of pain severity and progression in knee OA [22,23]. Thus, androgen decline may indirectly exacerbate joint loading and symptom expression.

Clinical trials evaluating testosterone therapy in women have demonstrated improvements in lean mass and muscle strength under supervised conditions [45,46]. However:

- OA-specific outcomes are rarely primary endpoints.
- Long-term safety data require careful stratification.

The evidence supports a plausible biomechanical benefit through muscle preservation. Direct disease-modifying claims in OA are not currently supported.

4. Vitamin D: Endocrine Regulation of Bone, Muscle, and Immunity

Vitamin D is a steroid hormone involved in immune modulation, bone remodelling, and muscle function [47,48]. Deficiency is prevalent in midlife and older women.

Associations include:

- Increased pro-inflammatory cytokine production
- Impaired muscle performance
- Increased falls risk
- Correlation with greater pain in some OA cohorts[49–51]

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Randomised trials of vitamin D supplementation in knee OA show mixed structural outcomes but more consistent improvements in muscle function when baseline deficiency is corrected [50].

Vitamin D optimisation should therefore be viewed as foundational musculoskeletal care rather than disease-specific OA therapy.

Hormone Therapy as a Disease-Environment Modulator

Menopausal hormone therapy (MHT) does not repair cartilage defects, reverse established osteophytes, or eliminate mechanical malalignment. Its potential relevance lies in modifying the biological environment in which osteoarthritis symptoms and functional decline evolve.

When appropriately indicated, individualised, and supervised, MHT may:

- Reduce chronic low-grade systemic inflammation
- Modulate IL-6 and TNF-α signalling
- Improve muscle mass and neuromuscular coordination
- Lower pain sensitisation thresholds
- Enhance rehabilitation response

Table 2. Hierarchy of Evidence for Hormonal Modulation in Knee Osteoarthritis-Related Outcomes in Midlife Women.

Outcome	Evidence Strength
Reduction in joint pain (selected women)	Moderate
Improvement in lean mass/strength (androgen-inclusive regimens)	Moderate
Reduction in falls risk (partly via bone/muscle effects)	Moderate
Prevention or reversal of structural OA	Limited / Inconsistent

Timing Hypothesis and Biological Window

Emerging literature supports a "timing hypothesis" in menopausal hormone therapy: initiation closer to menopause transition appears associated with more favourable systemic effects compared with late initiation [52–54].

From an orthopaedic perspective, this aligns with the concept of a musculoskeletal inflection period. If endocrine modulation influences inflammatory tone and neuromuscular resilience, earlier intervention within the transition window may yield greater functional benefit than delayed initiation after prolonged catabolic adaptation.

However, definitive OA-specific structural timing trials do not exist.

Risk Stratification and Therapeutic Boundaries

Hormone therapy is not universally appropriate. Clinical decision-making requires individualised risk–benefit assessment by qualified menopause specialists.

Established considerations include:

- Personal or high-risk history of hormone-sensitive malignancy
- Thromboembolic risk factors
- Cardiovascular profile
- Age and time since menopause onset
- Uterine status (endometrial protection requirements)
- Migraine and other vascular sensitivities

Modern position statements emphasise individualisation, dose optimisation, route of administration, and ongoing monitoring [52–55].

Failure to treat symptomatic hormonal deficiency may carry musculoskeletal costs, but inappropriate treatment carries systemic risk. Both realities must be acknowledged.

Orthopaedic Interpretation

The orthopaedic argument is not that hormone therapy "treats osteoarthritis."

It is that untreated endocrine decline may:

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- Amplify inflammatory tone
- Accelerate sarcopenic change
- Impair neuromuscular stability
- Increase pain sensitisation
- Reduce rehabilitation responsiveness

In this context, repeated mechanical intervention without biological optimisation may produce diminishing returns.

Hormonal biology does not replace biomechanics. It modifies the conditions under which biomechanics operate.

If menopause transition represents a period of altered inflammatory and neuromuscular equilibrium, then orthopaedic practice must adapt.

The question is no longer whether hormones are relevant to musculoskeletal physiology. The question is how orthopaedics integrates this knowledge into structured clinical pathways without exceeding scope of practice.

That is the focus of the next chapter.

Chapter 4

Implications for Orthopaedic Practice: Translating Hormonal Biology into Clinical Pathways

The integration of endocrine biology into osteoarthritis care does not require expansion of orthopaedic prescribing authority. It requires refinement of phenotyping, timing awareness, and structured collaboration.

Osteoarthritis management in midlife women must evolve from a purely structural model toward a biologically contextual model.

Traditional orthopaedic phenotyping emphasises:

- Alignment and mechanical axis
- Cartilage loss severity
- Meniscal integrity
- Subchondral sclerosis and bone marrow lesions
- Range of motion and instability

These remain essential. However, in midlife women—particularly during perimenopause—an additional biological layer frequently overlays structural findings.

An endocrine-aware phenotype may include:

- Disproportionate pain relative to radiographic severity
- Rapid escalation of symptoms over 1–3 years
- Diffuse stiffness beyond index joint
- Concomitant sleep disturbance
- Decline in muscle strength without major change in activity
- Central sensitisation features (widespread tenderness, reduced thresholds)[16,17]
- Recent menstrual irregularity or menopause transition symptoms[8]

This does not replace structural classification. It contextualises it. Failure to identify this phenotype risks repeated local intervention without systemic optimisation.

The Perimenopause Inflection Window in Clinical Decision-Making

Epidemiological data suggest that musculoskeletal pain prevalence increases during perimenopause and stabilises thereafter [8]. This pattern supports a transition window rather than linear degenerative accumulation.

From a clinical standpoint, this has several implications:

- Abrupt symptom escalation in a 45–55-year-old woman should not automatically be labelled "rapid structural OA progression."
- A biologically mediated inflammatory amplification may be contributing.
- Escalating mechanical interventions without endocrine assessment may be premature.

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This is particularly relevant in patients presenting with:

- New-onset bilateral knee pain
- Global stiffness and fatigue
- Reduced recovery from exercise
- Sleep fragmentation

Mechanical pathology may be present. But the biological substrate may have shifted.

Reinterpreting Treatment Resistance

In midlife women with knee OA, the following scenario is common:

- Appropriate physiotherapy prescribed
- Injection therapies performed
- Imaging-guided interventions delivered
- Temporary benefit, followed by recurrence

In many such cases, persistent low-grade inflammation, sarcopenic change, or endocrine-related neuromuscular decline may be undermining recovery capacity [5–7,34].

Inflammatory mediators such as IL-6 and TNF-α, upregulated in oestrogen-deficient states, impair tissue adaptation and perpetuate nociceptive sensitisation [24–26].

Repeated local intervention in a persistently pro-inflammatory environment may generate diminishing clinical returns.

This is not a patient compliance issue. It is a systems issue.

In this context Orthopaedic surgeons - without proper training- should not prescribe menopausal hormone therapy.

However, biologically literate orthopaedics includes**:**

A. Screening Awareness

Simple clinical prompts may identify relevant endocrine transition:

- Recent menstrual irregularity or cessation
- Vasomotor symptoms
- Sleep disturbance
- Unexplained muscle weakness
- Rapid change in pain phenotype

These questions require minimal time yet significantly refine phenotyping.

B. Defined Referral Pathway

Where appropriate, structured referral to:

- Gynaecologists with menopause expertise
- Endocrinologists
- Dedicated women's health menopause clinics

Collaboration should include shared outcome goals:

- Pain reduction
- Muscle strength preservation
- Functional recovery
- Delay of surgical intervention where appropriate

C. Parallel Optimisation

Endocrine assessment should occur in parallel with:

- Strength rehabilitation
- Load management
- Weight optimisation
- Vitamin D correction[47–50]

Integrated care enhances coherence. This is not integrative ideology. It is systems-based medicine.

In this context Joint preservation approaches—including:

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- Targeted rehabilitation
- Injection therapies
- Biologic/regenerative strategies
- Alignment procedures

However, Inflammatory amplification and neuromuscular decline might reduce responsiveness to conservative measures. [56,57]

If endocrine optimisation reduces inflammatory noise and improves muscle integrity, preservation strategies may:

- Demonstrate improved durability
- Achieve more sustained symptom control
- Delay transition to arthroplasty

Direct trial evidence linking hormone therapy to improved joint preservation outcomes remains limited. However, mechanistic coherence supports investigation.

Implications for Surgical Timing and Outcomes

Total knee arthroplasty and other reconstructive procedures correct structure but do not directly address:

- Systemic inflammatory tone
- Sarcopenia
- Central sensitisation

Persistent inflammatory amplification and muscle weakness may contribute to:

- Slower post-operative recovery
- Persistent pain despite technically successful surgery
- Reduced functional gains

Optimising muscle mass, sleep quality, inflammatory status, and metabolic health before surgery aligns with modern enhanced recovery principles. Endocrine optimisation, where indicated, may form part of that preparation. This remains an area for prospective study.

Research Directions

Osteoarthritis in midlife women cannot be fully understood through imaging alone. The menopause transition introduces measurable biological shifts in immune tone, neuromuscular function, and pain processing. These shifts influence how structural joint pathology is experienced and how patients respond to intervention.

Future research priorities include:

- Prospective cohort studies evaluating OA progression across menopause transition
- Stratified analyses of MHT timing relative to symptom onset
- Trials assessing musculoskeletal functional outcomes in endocrine-optimised vs non-optimised OA cohorts
- Biomarker-guided phenotyping of inflammatory OA subtypes
- Integration of muscle mass metrics into OA progression modelling

Without such data, mechanistic plausibility will remain ahead of clinical certainty.

Orthopaedics does not need to become endocrinology. But orthopaedics must become biologically literate.

Chapter 5

Conclusions and Future Directions

Osteoarthritis in midlife women should no longer be conceptualised as a purely mechanical consequence of ageing. Contemporary evidence supports a model in which structural degeneration, low-grade inflammation, neuromuscular decline, and endocrine transition interact dynamically [58–62].

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The menopause transition appears to represent a period of biological recalibration. During this window, shifts in oestradiol and related hormones influence immune signalling, muscle mass regulation, connective tissue behaviour, and pain sensitisation [24,63,64]. These changes do not independently "cause" osteoarthritis, but they may amplify symptom expression, reduce recovery capacity, and modify treatment responsiveness in women with existing or emerging joint pathology.

Current clinical evidence supports moderate confidence that appropriately indicated menopausal hormone therapy may reduce joint pain and improve aspects of musculoskeletal resilience in selected women [35]. Evidence supporting structural disease modification remains limited and requires further prospective study [31–33]. Precision in this distinction is essential.

For orthopaedic practice, the implication is pragmatic rather than ideological:

- Structural pathology must be assessed rigorously.
- Inflammatory and neuromuscular context must be recognised.
- Endocrine transition should be considered in phenotyping midlife women with disproportionate symptoms.
- Structured collaboration with menopause specialists may enhance functional outcomes.

Integrating hormonal biology into osteoarthritis care does not expand orthopaedic scope. It refines clinical judgement.

Future research should prioritise stratified cohorts across the menopause transition, timing-sensitive analyses of hormone therapy initiation, and functional musculoskeletal endpoints relevant to joint preservation and surgical outcomes.

Osteoarthritis management improves when biomechanics and biology are considered together. That integration represents progression—not reinvention—of orthopaedic medicine.

Disclaimer: This manuscript does not propose hormonal prescription by orthopaedic surgeons. It outlines the musculoskeletal consequences of hormonal decline across the menopause transition and argues for structured collaboration with clinicians specialised in women's hormonal health. Any discussion of menopausal hormone therapy (MHT/HRT) refers to medically supervised, individualised care under established women's health guidelines and risk stratification.

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