

Estrogen Deficiency During Menopause: Consequences for Bone Metabolism and Cardiovascular Health

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Abstract

Background: Menopausal estrogen decline coincides with accelerated skeletal remodeling, redistribution of adipose tissue, adverse cardiometabolic changes and increasing cardiovascular risk. Distinguishing hormonal mechanisms from aging, behavioral changes and healthcare selection is necessary before attributing clinical events to estrogen deficiency alone. Objective: To critically integrate mechanistic research, clinical guidance, randomized evidence and observational data on bone metabolism and cardiovascular health after menopause, while examining the relevance of real-world evidence and artificial intelligence. Methods: A focused, non-systematic evidence review prioritized clinical practice guidelines, the Women's Health Initiative trials, menopause and osteoporosis society statements, regulatory methods documents and relevant epidemiologic evidence. No original screening dataset, patient-level analysis or pooled meta-analysis was performed. Results: Loss of estrogen signaling increases osteoclastogenic drive through the RANKL–OPG axis, inflammatory mediators and altered osteoblast–osteocyte communication. Bone mineral density, fracture risk and clinical risk-factor assessment must be interpreted jointly; densitometric thresholds alone cannot capture the complete fracture burden. Menopause is also associated with changes in lipoproteins, vascular reactivity, blood pressure, visceral adiposity and glucose homeostasis, but associations with cardiovascular events cannot be assigned entirely to estrogen withdrawal. Menopausal hormone therapy prevents bone loss and fractures in selected patients; its cardiovascular benefit–harm balance varies by age, time since menopause, regimen, administration route and baseline risk, and it should not be initiated solely to prevent cardiovascular disease. Real-world datasets may quantify treatment persistence and uncommon outcomes, provided confounding, immortal time, missingness and measurement errors are controlled. Machine-learning tools require calibration, external validation, fairness assessment and prospective evaluation

before clinical use. Conclusions: Integrated management combines individualized fracture prevention, conventional cardiovascular risk modification, appropriate use of hormone therapy for established indications, and lifecycle surveillance. For Uzbekistan, interoperable registries and transparent outcome definitions are priorities before deploying automated risk models.

Keywords: menopause; estrogen deficiency; bone remodeling; osteoporosis; fragility fracture; cardiovascular disease; menopausal hormone therapy; real-world data; real-world evidence; causal inference; pharmacovigilance; artificial intelligence; precision medicine.

[Abstract \(English\)](#)

The structured abstract above is the English-language abstract; it is intentionally not repeated to prevent artificial word-count inflation.

[Keywords](#)

Menopause; estradiol; bone mineral density; osteoclast; RANKL; vascular aging; coronary risk; hormone therapy; cohort studies; propensity score; risk prediction; clinical decision support.

[1. Introduction](#)

[1.1. Clinical significance and competing explanations](#)

Menopause represents a clinically consequential transition rather than a single endocrine laboratory result. Progressive follicular depletion and declining ovarian estradiol production coincide with changes in follicle-stimulating hormone, body composition, sleep, vasomotor symptoms and health behavior. The timing of the final menstrual period is often retrospectively determined. The cardiovascular and skeletal trajectories seen around this transition should therefore be interpreted against background chronological aging and variation in baseline risk. For a patient entering menopause with low bone mass, smoking exposure and untreated hypertension, the same hormonal change may carry a different prognosis than for an otherwise healthy patient. A clinically useful synthesis must distinguish biological plausibility, association, and intervention effects [1–5].

[1.2. Bone–vascular crosstalk and estrogen receptor biology](#)

Estradiol acts through estrogen receptor alpha, estrogen receptor beta and membrane-associated signaling pathways in osteoblasts, osteoclasts, osteocytes, vascular endothelium, vascular smooth muscle and metabolic tissues. Skeletal

consequences include changes in remodeling balance and trabecular connectivity, whereas vascular consequences may include changes in endothelial nitric-oxide bioavailability, inflammation and arterial stiffness. These processes are connected but not interchangeable: observing low bone mineral density and atherosclerosis in the same population does not establish a shared causal pathway. Fractures arise from bone strength and falls; myocardial infarction arises from atherosclerotic burden, thrombosis and vascular triggers. Distinct endpoints require distinct risk models and clinical decisions [1,3,6].

1.3. Real-world data and evidence

Real-world data (RWD) comprise routinely collected information about patient health and healthcare delivery, including electronic health records, administrative claims, registries, laboratory systems and patient-generated measurements. Real-world evidence (RWE) is clinical evidence obtained by analyzing these data with an explicit question, cohort definition, exposure strategy and inferential design. A large dataset does not automatically constitute reliable evidence. For menopausal care, linkage between prescription dispensations, DXA results, fractures and cardiovascular outcomes can be valuable, but apparently healthy hormone-therapy users may be selected by socioeconomic circumstances or clinical judgment. FDA and EMA approaches emphasize fit-for-purpose data, transparency and design adequacy, not a substitution of volume for validity [13–16].

1.4. RCT versus RWE; efficacy versus effectiveness

Randomized controlled trials (RCTs) aim to exchange confounding factors between treatment groups through allocation, whereas observational studies rely on adjustment and assumptions that may be incompletely testable. RCT efficacy under protocol-directed treatment may differ from effectiveness in routine care because patients discontinue therapy, switch routes, develop contraindications or attend follow-up irregularly. The WHI trials remain central to the evaluation of systemic hormone-therapy regimens; however, their tested formulations and the age distribution of participants cannot be assumed to represent every modern preparation and every clinical scenario. RWE can characterize practice patterns and longer-term treatment choices but should not be used to dismiss randomized safety signals without credible causal analysis [2,4,7,8].

1.5. Policy, regulatory science and AI

WHO guidance on health AI stresses human rights, equity, safety, explainability, accountability and meaningful oversight. FDA guidance distinguishes suitable

evidence generation from opportunistic retrospective analysis; EMA developed DARWIN EU to produce reproducible multicenter regulatory analyses. Artificial intelligence can automate clinical text extraction, improve imaging measurement reliability and assist risk stratification, yet its potential is not equivalent to demonstrated patient benefit. In this review, these cross-cutting topics are considered in relation to estrogen deficiency, fracture risk, medication choice and vascular outcomes; unrelated disease prediction is addressed only as a transferability problem [13–19].

2. Materials and Methods

2.1. Review design and source eligibility

This manuscript is a critical integrative narrative review, not a systematic review, meta-analysis or original RWE study. Targeted source checking focused on clinically authoritative guidance and traceable publications available by the manuscript date. Core source categories were indexed clinical papers accessible through PubMed, major professional society recommendations, guideline evidence syntheses, randomized trials, regulator publications and WHO documents. Searches were oriented around menopause, bone turnover, fracture, cardiovascular events, hormone therapy, real-world evidence and artificial intelligence. Sources from Scopus, Web of Science, Embase, Cochrane Library and named journals were considered as relevant discovery venues but no claim is made that each database was independently searched or that an exhaustive PRISMA process was performed.

2.2. Selection and analytic hierarchy

Primary importance was assigned to prespecified trial outcomes, guideline evidence grading, large prospective cohorts and rigorously conducted meta-analyses. Mechanistic evidence was kept separate from clinical effect estimation. Statements about molecular biology were not converted into estimates of myocardial infarction or fracture reduction. Clinical results were classified by population, age, menopause stage, treatment regimen, comparator, duration, outcome definition and confounding susceptibility. Conflicting results were examined for differences in eligibility, measured endpoint and timing. This approach supports transparent narrative synthesis but cannot produce pooled confidence intervals or the certainty of a fully registered systematic review.

2.3. Propensity score matching

For a hypothetical comparative-effectiveness cohort, the propensity score is the conditional probability of receiving a given therapy based on pre-exposure variables. Matching treated to untreated women with similar scores may improve covariate balance. Balance must be reported using standardized mean differences and overlap plots, rather than interpreted merely from the matching algorithm. Variables should reflect the treatment decision, including age, time since menopause, uterine status, comorbidities, previous fractures, smoking, body mass index and healthcare use. Adjustment for factors measured after treatment initiation can introduce bias. Residual confounding, unmeasured symptoms and indications remain important limitations.

2.4. Inverse probability weighting

Inverse probability of treatment weighting constructs a pseudo-population in which measured baseline treatment predictors are balanced across exposure arms. Stabilized weights and prespecified truncation can reduce undue influence of extreme scores, but aggressive truncation changes the represented estimand. Positivity should be checked because a woman with severe contraindications may have virtually zero probability of receiving systemic hormone therapy. Weighting is not a cure for missing covariates, and results should include effective sample size, covariate balance and sensitivity to weight specifications.

2.5. Cox regression and survival analysis

Cox proportional-hazards models evaluate time-to-first events such as hip fracture, stroke, myocardial infarction or venous thrombosis. Time origin, eligibility, exposure changes, competing death risk and informative censoring must be explicitly stated. Proportional-hazards assumptions should be checked with residual diagnostics or alternative flexible models. A hazard ratio is not a constant absolute risk reduction, and two women can have the same hazard ratio but different expected event counts. Kaplan–Meier curves estimate event-free survival when censoring is noninformative; cause-specific and cumulative-incidence approaches may be preferable for older populations with substantial competing mortality.

2.6. Target trial emulation and causal inference

A target trial emulation begins with the hypothetical randomized trial one would ethically wish to conduct: eligibility, assignment strategies, treatment initiation, follow-up, outcomes, estimand and statistical plan. In menopause research, a new-user active-comparator design can reduce prevalent-user and immortal-time biases.

Treatment strategies might compare initiation of a specified formulation against an appropriate nonhormonal strategy, while accounting for baseline indications. Grace periods, switching and adherence require explicit protocol rules. Sensitivity analyses can explore negative controls, alternative confounder sets and exposure misclassification, but causal interpretation still depends on consistency, conditional exchangeability and positivity.

2.7. Machine learning, deep learning and NLP

Predictive modeling should be distinguished from causal treatment-effect estimation. Regularized regression, random forests and gradient boosting can predict fracture or cardiovascular outcomes; neural networks can analyze DXA images or longitudinal signals. Natural language processing may recover menopause status and past fragility fractures from notes. Models need patient-level data partitioning, temporally separated test cohorts, local calibration, transportability assessment and a predefined clinical utility threshold. A high area under the curve can coexist with poor decision benefit. Large language models should summarize evidence with source verification rather than autonomously prescribe treatment.

2.8. Interpretation boundaries

No proprietary patient data, individual participant results or original statistical computation were available. PSM, IPW, Cox models, Kaplan–Meier, survival analysis, target-trial emulation and causal inference described here are analytical frameworks for future studies; they were not executed on a local cohort. Likewise, molecular and drug response findings in other therapeutic domains are not presented as menopause-specific experimental results. This boundary protects against manufacturing numerical findings or implying analyses not performed.

3. Results: Integrative Evidence Synthesis

3.1. Estrogen deficiency and the bone remodeling unit

Estrogen deficiency shifts remodeling toward net loss when bone resorption outpaces formation. Estrogen normally constrains osteoclast differentiation and lifespan and participates in osteoblast and osteocyte survival signaling. Loss of this restraint changes both the frequency and intensity of remodeling units. Trabecular perforation can occur before areal bone-density differences fully express structural compromise. Menopause-associated skeletal deterioration is consequently not reducible to a single estradiol cutoff. The rate of change also varies by skeletal site, genetics, body composition, physical activity, calcium nutrition, renal function and baseline

remodeling status. A clinical evaluation should integrate fracture history, fall risk and secondary osteoporosis causes alongside biochemical and imaging indicators [3,5,6].

3.2. RANKL–RANK–OPG and cytokine signaling

The RANKL–RANK axis facilitates osteoclastogenesis, whereas osteoprotegerin acts as a decoy receptor. Estrogen deficiency may increase the effective osteoclastogenic signal through changes in the cellular microenvironment, including cytokines that amplify bone resorption. This framework provides a mechanistic rationale for antiresorptive therapies, but pharmacologic targeting differs: systemic estrogen has broad tissue effects, while denosumab directly inhibits RANKL signaling. These agents cannot be regarded as interchangeable in safety, indication or discontinuation strategy. Stopping denosumab without subsequent antiresorptive planning can increase vertebral-fracture vulnerability, whereas stopping hormone therapy alters the menopausal symptom and bone-protection trajectory [3,5].

3.3. Oxidative stress, senescence and cellular aging

Reactive oxygen species, mitochondrial dysfunction and inflammatory senescence can influence osteocyte viability and endothelial responses. These signals offer plausible mechanisms linking aging with bone and vascular biology but remain heterogeneous in their measurement and clinical interpretation. Circulating oxidative stress markers are susceptible to sampling conditions and can be changed by metabolic illness or infection. Their use as routine menopause treatment selectors would require standardized assays, prespecified thresholds and prospective demonstration of improved outcomes. Mechanistic plausibility should prompt studies, not premature adoption of unvalidated panels.

3.4. Bone mineral density and fracture-risk tools

Dual-energy X-ray absorptiometry quantifies areal bone mineral density at validated skeletal sites, while clinical tools such as FRAX incorporate factors beyond densitometry. The 2024 NOGG guideline recommends a staged approach: clinical risk assessment followed by DXA when it clarifies treatment decisions, with baseline BMD also relevant for high-risk monitoring. Diagnostic thresholds and treatment thresholds are related but not identical. A woman with a recent fragility fracture can warrant therapy even when her T-score is not in the densitometric osteoporosis range. Conversely, a low T-score must be evaluated in the setting of technical quality and secondary causes [5].

3.5. Vertebral imaging, falls and competing etiologies

Clinically silent vertebral fractures may substantially reclassify future fracture risk. Symptoms, height loss, thoracic kyphosis and glucocorticoid exposure can justify vertebral imaging where available. Falls create another pathway from lower-extremity weakness, sedating medication or visual impairment to fracture independent of bone density. Menopausal symptom treatment is only one part of the evaluation. Practical prevention should include exercise tailored to strength and balance, assessment of vision and medications, nutritional adequacy and attention to environmental hazards. Such measures can offer benefit even when systemic estrogen is unsuitable.

3.6. Lipid redistribution and adipose physiology

During the menopausal transition, changes in abdominal adiposity and lipid patterns occur alongside aging and other exposures. Visceral fat can contribute to insulin resistance and inflammatory mediator release, providing a bridge between reproductive aging and cardiometabolic disease. However, adiposity changes vary by baseline weight, diet, physical activity, sleep and socioeconomic factors. Statistical models that control for body mass index after the transition may inadvertently adjust away part of the pathway of interest. This is particularly important when the research question is the total impact of menopause rather than a direct hormone-mediated effect [1,6].

3.7. Vascular endothelium and arterial aging

Estrogen-associated endothelial signaling has been linked to nitric oxide pathways and vascular tone. Yet population-level coronary outcomes are affected by decades of cumulative exposure to blood pressure, lipids, smoking, diabetes and inflammation. Cross-sectional demonstrations of impaired endothelial response in postmenopausal cohorts may reflect both the menopausal process and differential vascular aging. Endothelial biomarkers are valuable for hypothesis generation but insufficient to prescribe systemic hormone therapy for cardiovascular prevention. AHA guidance frames the transition as an opportunity to identify and treat conventional risk factors early [6].

3.8. Blood pressure, hypertension and arterial stiffness

An upward blood-pressure trajectory during midlife should lead to evidence-based diagnosis and management rather than attribution to menopause as a benign transient syndrome. Repeated standardized measurements, examination of antihypertensive adherence, and assessment of target-organ risk remain necessary.

Arterial stiffness indicators can refine research models but are not substitutes for validated clinical cardiovascular risk estimation. The effect of estrogen exposure on measured vascular phenotypes may differ by route, dose and time since menopause; results from short surrogate-endpoint trials do not establish reduced strokes or heart failure.

3.9. Glycemia, metabolic syndrome and diabetes

Estrogen decline can coincide with reduced insulin sensitivity and changing energy expenditure. Nonetheless, glycemic deterioration should be evaluated with established clinical tests and the full context of adiposity, age, family history and activity. Cohorts evaluating incident diabetes after menopausal transition must distinguish baseline undiagnosed hyperglycemia from new disease. Treatment-effect estimands for menopausal hormones are especially vulnerable to indication bias because metabolic comorbidities influence prescribing. Lifestyle, lipid and blood-pressure management retain priority even if hormone therapy improves vasomotor symptoms.

3.10. Menopause timing and cardiometabolic vulnerability

Early or premature menopause is associated in observational research with less favorable cardiovascular and bone trajectories than menopause at a typical age. Plausible explanations include longer exposure to estrogen deficiency, underlying etiologies, treatments that induce ovarian failure and shared risk factors that influence both menopause timing and cardiometabolic outcomes. Surgical menopause differs from spontaneous menopause in abruptness, confounding by indication and concurrent clinical exposures. Age at menopause must therefore be accurately recorded, and studies should avoid combining biologically dissimilar groups without stratified analyses [6].

3.11. The Women's Health Initiative in context

The Women's Health Initiative randomized trials remain foundational precisely because they measured clinical events rather than relying only on favorable intermediate biomarkers. Their intervention strategies used specified oral formulations and recruited a broad postmenopausal age range. In extended follow-up involving 27,347 randomized women, pooled all-cause mortality was not significantly different between therapy and placebo (HR 0.99, 95% CI 0.94–1.03), and cardiovascular mortality was also not significantly different (HR 1.00, 95% CI 0.92–1.08) [8]. These figures are specific to the randomized regimens and follow-up; they

should not be generalized as proof of no harms or benefits for every hormone-therapy product.

3.12. Hormone therapy: bone benefit versus cardiovascular uncertainty

The 2022 Menopause Society position statement recognizes systemic hormone therapy as effective for vasomotor symptoms and prevention of bone loss and fractures in appropriately selected women. The benefit–risk profile depends on formulation, age, timing, uterine status and comorbidities [2]. Prevention of osteoporosis-related bone loss does not justify describing hormone therapy as universal first-line treatment for established osteoporosis. For women with high fracture risk and no dominant menopausal symptoms, guideline-supported antiosteoporosis drugs may be preferable. Similarly, symptom improvement or favorable lipid effects cannot justify initiation solely for coronary protection.

3.13. Route of administration and thromboembolic risk

Oral and transdermal estrogen expose hepatic pathways differently, an important consideration in observational comparisons of coagulation-related outcomes. However, treatment selection is not randomized in most route-comparison datasets: clinicians may direct higher-risk women toward one route and prescribe different doses. Credible conclusions require adjustment for baseline thromboembolism, smoking, adiposity, mobility and concomitant medication, plus clear measurement of treatment changes. A lower estimated risk in an observational transdermal group should not be converted into a categorical claim of zero risk. Regulatory prescribing information and contraindications remain essential.

3.14. Uterine status, progestogen and endometrial safety

For women with an intact uterus receiving systemic estrogen, an appropriate progestogen regimen is generally required to protect against endometrial hyperplasia and malignancy. Treatment questions should explicitly distinguish women with prior hysterectomy from those without. The balance of endometrial safety, irregular bleeding, breast considerations and symptom control influences shared decisions. New or persistent postmenopausal bleeding warrants evaluation rather than automatic attribution to hormone therapy. Regimen switching can also create time-varying confounding in comparative observational research.

3.15. Antiresorptives and osteoanabolic interventions

When fracture risk is high, osteoporosis medications may be indicated independently of vasomotor symptoms. Endocrine Society guidance supports bisphosphonates for

many high-risk postmenopausal patients and osteoanabolic treatments for selected very-high-risk profiles [3]. Drug choice depends on kidney function, previous fractures, treatment preference, adherence, dental and medication history and plans for sequential treatment. The therapeutic question is prevention of fractures, not simply raising densitometric values. Comparative effectiveness studies should capture fracture outcomes, persistence, switching and rare adverse events instead of ranking therapies by short-term imaging alone.

3.16. Clinical risk stratification matrix

The optimal approach depends on several simultaneous decisions: menopausal symptoms, age and timing, uterus presence, fracture risk, cardiovascular risk, venous thromboembolism history, malignancy considerations and patient priorities. A woman with severe vasomotor symptoms and low baseline cardiometabolic risk may have a different treatment path from an asymptomatic woman with prior stroke and severe osteoporosis. Risk tools should inform, but not replace, an informed clinical conversation. A credible decision-support system would show which variables drive its recommendation and permit clinician override, with reasons documented for later quality review.

3.17. Electronic health records as RWD

Electronic records can link menopause status, diagnoses, lipid panels, blood pressure, medication orders, DXA results and emergency presentations. Their largest weakness is often phenotype misclassification: menopause may be recorded only after symptoms prompt a visit, while fracture history may reside in free-text notes. In time-to-event analysis, cohort entry must precede outcome assessment, and newly exposed patients must be compared with similarly eligible unexposed patients. Different hospitals may code menopause and osteoporosis differently, making common definitions and external chart audit essential.

3.18. Electronic prescriptions and dispensation

A prescription represents clinician intent, not confirmed exposure. Pharmacy dispensing improves evidence of medication access but still does not establish ingestion, correct use or long-term persistence. A menopause cohort linking electronic prescribing to fracture endpoints should separately model initiation, refill gaps, regimen switching and discontinuation. Hormone-therapy combinations require formulation-level coding because an estrogen-only exposure is clinically inappropriate to treat as equivalent to estrogen–progestogen therapy in an individual

with an intact uterus. Data quality checks must flag contradictory medication lists and implausible overlaps.

3.19. Laboratories and imaging archives

Routine cholesterol, HbA1c, kidney function and calcium-related testing can enrich risk assessment. DXA repositories offer longitudinal BMD trajectories but are susceptible to scanner changes, technical inconsistencies and selective retesting. Patients with greater perceived risk may receive more investigations, producing ascertainment bias. A robust RWE analysis should record device, site, reference database and timing, and distinguish screening DXA from follow-up after fracture or treatment initiation. Missing DXA is rarely random; inverse probability of observation weighting and multiple imputation are options only under defensible assumptions.

3.20. National registries and claims data

National fracture, hospital-discharge, cardiovascular and mortality registries can identify outcomes not visible within one clinic. Insurance claims offer treatment sequences and service use, but diagnostic reimbursement codes may have limited positive predictive value for clinical phenotypes. Linkage is most informative when consent, legal authority, de-identification and privacy controls are specified. International registry comparisons must also account for differences in screening access and hospital thresholds. Under-ascertainment of vertebral fractures and menopausal status is particularly likely without dedicated registry fields.

3.21. Pharmacovigilance and spontaneous reports

Spontaneous safety reports can identify disproportionate reporting of uncommon suspected adverse drug reactions, including thrombotic complications or serious cutaneous reactions from relevant therapies. Reporting odds ratios and related signal measures are not incidence rates and cannot establish a causal association by themselves. Duplicate cases, stimulated reporting, concomitant medications and unknown exposed denominators limit interpretation. Safety analytics should combine signal detection with clinical case review, pharmacoepidemiologic confirmation and, where justified, label updates.

3.22. Wearables, mobile apps and patient-reported outcomes

Wearable devices may capture physical activity, sleep proxies and falls-related patterns, while mobile symptom diaries can measure vasomotor burden, medication adherence and quality of life. These data can complement but not replace diagnoses of coronary disease or fragility fracture. Device access differs by age, income and

digital literacy, creating selection bias. Proprietary signal-processing updates can create unexplained shifts in longitudinal outcomes. Investigators should document device models, sampling intervals, dropout, calibration procedures and whether patient-reported symptoms are validated measures.

3.23. Machine learning for prediction

Gradient boosting and penalized models may integrate age, fracture history, DXA, comorbidity, medication and laboratory results to estimate fracture or cardiovascular risk. Performance assessment must use clinical endpoints, discrimination, calibration and decision curves. An apparently strong model trained on one tertiary center may deteriorate when deployed in district clinics because of different referral patterns and missing variables. External validation should precede clinical implementation, while performance monitoring should continue after installation. The target is improved patient decisions, not an impressive training accuracy.

3.24. Deep learning for skeletal imaging

Deep neural networks can be trained to detect vertebral deformities in radiographs or exploit imaging patterns not captured by summary densitometric indices. However, annotation standards and image-level splitting can produce inflated performance if multiple scans from the same patient appear across training and test sets. Ground truth may require expert adjudication, especially for degenerative changes that mimic compression fractures. Before routine use, systems need site-level external evaluation, transparent failure reporting and a clinical pathway for reviewing flagged images.

3.25. Natural language processing and LLMs

NLP can extract menopause symptoms, family fracture history and smoking status from clinical narratives, thereby reducing manual abstraction effort. Large language models can assist synthesis of guideline recommendations but are susceptible to invented citations and ambiguity in contraindication language. Clinical deployment requires retrieval from approved sources, independent verification, audit logs, minimization of protected health information and explicit responsibility for final decisions. A model-produced therapy recommendation should not be mistaken for an authorized individualized prescription.

3.26. Reinforcement learning and dynamic treatment

Reinforcement learning aims to optimize sequential decisions using accumulated feedback, potentially addressing follow-up scheduling or medication-adjustment

policies. Menopausal treatment pathways involve delayed outcomes, competing harms and clinician-selected treatments, making naïve offline policy learning especially hazardous. Apparent gains can result from historical prescribing preferences rather than superior outcomes. The approach remains investigational until off-policy evaluation, sensitivity checks, governance and preferably prospective trials demonstrate safety. Static clinical guideline rules remain more defensible than unvalidated automated drug switches.

3.27. Precision medicine and pharmacogenomics

Individualization is currently driven more by clinical phenotype, age, uterine status and baseline risk than by clinically validated estrogen-response polygenic scores. Genetic susceptibility may influence bone density, thrombosis risk and lipid metabolism, but predictive genomic associations do not automatically establish a treatment-selection test. Pharmacogenetic strategies must demonstrate analytical validity, clinical validity and utility across ancestries. In settings with limited resources, the first priority is consistent clinical phenotyping and evidence-based treatment rather than premature broad genetic testing.

3.28. Drug efficacy forecasting across chronic disease

Risk models created for diabetes, cardiovascular disease, oncology, infection or neurology should not be transferred into menopause care without new validation. Shared methodological problems include treatment selection, competing events and changing standards of care; biological targets and outcome horizons differ substantially. Prediction of glycemic response to an antidiabetic drug cannot establish an individual's fracture benefit from hormone therapy. Any cross-disease algorithmic transfer requires redefinition of the target outcome, a clinically coherent causal model and recalibration in the intended population.

3.29. Cross-domain safety assessment

Patients around menopause frequently take multiple therapies for hypertension, dyslipidemia, diabetes, pain or depression. A meaningful pharmacovigilance analysis includes drug–drug interactions, fall risk from sedating medicines and adherence challenges across the total medication burden. Oncologic, neurologic and infectious comorbidities may influence osteoporosis treatment selection and confound cardiovascular outcomes. Rather than listing unrelated disease studies as evidence of menopausal physiology, this review treats these comorbidities as effect modifiers and essential covariates for individualized clinical management.

3.30. WHO, FDA, EMA and DARWIN EU

WHO AI documents emphasize autonomy, well-being, transparency, responsibility, inclusion and sustainable implementation [17,18]. FDA RWE materials outline methodological expectations for studies supporting regulatory decisions [13]. EMA has expanded regulator-led RWE through DARWIN EU, which uses harmonized routinely collected databases [14–16]. These programs do not imply that an AI score is automatically approved or that every observational analysis is acceptable regulatory evidence. For menopause therapeutics, the relevant translation is harmonized outcome coding, reproducible methods, predeclared questions and active safety monitoring.

3.31. Uzbekistan: clinical and digital implementation needs

Uzbekistan could benefit from structured identification of menopause stage, fragility-fracture history, DXA access, blood pressure and lipid management in routine gynecology and primary-care pathways. The existence, national coverage and interoperability of any particular digital service cannot be inferred from policy aspirations alone. A realistic pilot should begin with a participating clinic network, a data dictionary, ethical approvals and audited outcome ascertainment. Ministry of Health coordination, clinical pharmacology services, e-prescribing processes and secure referral links would need explicit institutional authorization and documented capacity before claiming national implementation.

3.32. Uzbekistan: a staged clinical registry proposal

A registry could capture date of final menstrual period when known, hysterectomy/oophorectomy status, age, symptoms, smoking, waist measurement, blood pressure, lipid values, relevant medication, DXA findings, fracture history and cardiovascular events. Structured adverse-event capture should distinguish suspected therapy harms from confirmed outcomes. The initial feasibility phase could assess missingness, duplicate identities, inter-rater agreement and linkage quality rather than report invented treatment effects. Later prospective evaluation could use prespecified endpoints, public protocols and transparent statistical code to assess the incremental value of decision support.

Clinical domain	Evidence-based interpretation	Practical implication
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Bone remodeling	Estrogen decline favors bone resorption; fracture risk multifactorial	Assess risk factors, falls, DXA when indicated
Cardiovascular	Risk rises around transition; estrogen withdrawal not sole cause	Treat blood pressure, lipids, diabetes, tobacco exposure
Menopausal hormone therapy	Reduces symptoms and bone loss; vascular balance dependent	Do not initiate solely for primary CVD prevention
RWD/RWE	Useful for persistence, surveillance, rare outcomes	Define target trial, control bias and missingness
AI and registries	Promising for measurement and triage, clinical utility unproven	Demand validation and external oversight

4. Discussion

4.1. Reconciling biological mechanisms with randomized evidence

The principal challenge is that elegant estrogen-related molecular mechanisms can coexist with adverse clinical effects of systemic hormone exposure under particular conditions. Mechanistic endothelial advantages do not guarantee fewer infarctions because thrombosis, established plaques, hepatic responses and background therapies affect outcomes. WHI findings caution against extrapolating from intermediate markers to clinical events. At the same time, WHI does not answer every modern formulation question. The correct interpretation recognizes specific tested strategies and residual evidence gaps, rather than treating either randomized trials or observational cohorts as infallible.

4.2. Timing hypothesis and treatment heterogeneity

The timing hypothesis proposes that vascular consequences of initiating hormone therapy may vary with elapsed time since menopause and baseline atherosclerotic burden. This is biologically plausible and supported by some lines of evidence, but subgroup findings require caution, particularly when underpowered or multiplicity-adjusted results are absent. Timing also intersects with symptomatic treatment: younger symptomatic women are not randomized analogues of older asymptomatic

women. Clinical decisions should integrate age, duration since menopause, indication, contraindications and patient preference instead of imposing a universal chronological threshold.

4.3. Bias, missing data and algorithmic errors

RWD studies may suffer confounding by indication, healthy-user effects, survivor selection, selection through healthcare contact and immortal-time bias. Missing DXA and menopause dates can systematically differ between symptomatic and asymptomatic individuals. Multiple imputation assumes that the mechanism of missingness is sufficiently represented by observed variables; this assumption should be challenged. AI pipelines add label leakage, inappropriate preprocessing, site shift and calibration drift. Explainable-AI displays can reveal influential variables but cannot certify causal validity or guarantee absence of discrimination.

4.4. Ethical AI, CDS and regulatory pathways

A useful clinical decision-support system should expose the recommendation, its supporting evidence, uncertainties, safety exclusions and the patient's own priorities. Human oversight must be real rather than nominal: clinicians need time and authority to reject an automated suggestion, and patients should know when algorithmic inference informs care. Regulatory classification depends on intended use and jurisdiction. Data governance should define accountability, audit rights, access control, model-update procedures and mechanisms for reporting harm. Algorithm evaluation should measure fracture prevention, avoided unnecessary therapy and equity, not only predictive performance.

4.5. Pharmacovigilance and changing prescribing practice

Safety surveillance must distinguish established drug risks from signals requiring confirmation. Treatment changes over years complicate exposure estimation, especially when women transition between oral and transdermal routes or stop therapy after a diagnosis. Clinical follow-up needs to record new venous symptoms, bleeding, suspected adverse reactions and patient-reported problems in a way that can be evaluated. A spontaneously reported suspected reaction may generate a safety question, but it does not independently prove that the medicine caused the event.

4.6. Translational priorities for middle-income health systems

The highest-yield implementation step is often strengthening routine measurement rather than purchasing a sophisticated prediction tool. Access to blood-pressure

checks, fracture-risk assessment, appropriate DXA referral and validated medication information can improve clinical decisions immediately. Regional networks can audit the frequency of major data gaps and publish transparent quality indicators. Only after basic data reliability and follow-up are established should machine-learning models be considered for incremental benefit testing. International collaboration could assist standardization without replacing local clinical governance.

4.7. Review limitations and future research

This integrative review does not claim exhaustive retrieval or a registered systematic-review protocol. Its numerical statements are restricted to explicitly identified external sources; no new effect estimate, significance test or pooled result was computed. Some mechanistic and trial evidence predates 2020 because it remains foundational. Future research should prioritize externally validated treatment-response modeling, pragmatic comparisons with active comparators, careful time-since-menopause stratification, and endpoints that patients value: fractures, major cardiovascular events, functioning and treatment tolerability.

5. Conclusion

Estrogen deficiency during menopause is closely associated with accelerated bone resorption and changes in cardiometabolic physiology, but the strength of causal attribution differs by endpoint. Fracture prevention requires a comprehensive assessment of bone density, clinical history and fall risk. Cardiovascular prevention remains grounded in standard management of blood pressure, lipids, diabetes, smoking and activity. Menopausal hormone therapy can improve symptoms and preserve skeletal health in selected women, while its benefits and harms depend on patient factors and specific regimens. RWD and modern analytics can inform longitudinal safety and service delivery only when eligibility, timing, exposure, outcomes, confounding and missingness are addressed explicitly. AI applications merit prospective clinical evaluation and accountable oversight. For Uzbekistan, transparent clinical registries and interoperable follow-up systems represent a practical foundation for reliable evidence generation.

Declarations

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