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REVIEW

Bone Health During Adjuvant Aromatase Inhibitor Therapy in Non-Metastatic Hormone Receptor-Positive Breast Cancer: from Pathophysiology to Evidence-Based Prevention and Management

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Abstract

Introduction: Aromatase inhibitors (AIs) are the cornerstone of adjuvant endocrine therapy for postmenopausal women with hormone receptor-positive early breast cancer. Although these agents substantially reduce recurrence, profound estrogen deprivation accelerates bone remodeling, leading to bone mineral density (BMD) loss and increased fracture risk. **Objective:** This review critically summarizes current understanding of AI-induced bone loss, integrating evidence on epidemiology, pathophysiology, fracture risk assessment, preventive strategies, pharmacological interventions, and clinical guidelines. **Methods:** A comprehensive literature review was performed using PubMed/MEDLINE, Scopus, and Google Scholar, prioritizing randomized controlled trials, meta-analyses, systematic reviews, and contemporary guidelines. **Results:** AI therapy induces accelerated bone loss exceeding physiological postmenopausal depletion, predominantly affecting trabecular-rich sites. While dual-energy X-ray absorptiometry remains the standard for monitoring BMD, complementary tools including trabecular bone score, FRAX, and bone turnover biomarkers improve identification of high-risk patients. Randomized trials demonstrate that bisphosphonates and denosumab effectively prevent AI-associated bone loss, with selected agents providing additional reductions in recurrence. Lifestyle modification, calcium and vitamin D optimization, and individualized risk stratification remain essential components of multidisciplinary management. **Conclusions:** Bone health preservation should be considered fundamental to adjuvant endocrine therapy. Contemporary management requires individualized fracture risk assessment, early identification of high-risk patients, evidence-based implementation of interventions, and multidisciplinary collaboration.

Keywords: Breast cancer, Aromatase inhibitors, Bone health, Osteoporosis, Bisphosphonates, Denosumab, Survivorship

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Introduction

Global Burden of Breast Cancer

Breast cancer remains the most frequently diagnosed malignancy and the leading cause of cancer incidence among women worldwide, representing a major global health challenge. According to GLOBOCAN 2022, more than 2.3 million women are diagnosed with breast cancer annually, accounting for approximately one-quarter of all female cancers. Despite considerable geographic variation in incidence, mortality, and access to healthcare, breast cancer continues to impose an increasing clinical and socioeconomic burden across both developed and developing countries [1].

Over the past two decades, improvements in population-based screening, molecular classification, multidisciplinary treatment, and supportive care have substantially reduced breast cancer mortality in many high-income countries. However, demographic aging, increasing life expectancy, obesity, delayed childbearing, reduced parity, and lifestyle-related risk factors continue to contribute to rising disease incidence globally [2, 3]. Consequently, an expanding population of breast cancer

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survivors requires long-term management of treatment-related adverse effects that may significantly affect quality of life and functional independence.

Among the recognized molecular subtypes, hormone receptor-positive (HR-positive) disease represents the largest proportion of newly diagnosed breast cancers, emphasizing the central role of endocrine therapy in contemporary breast cancer management [4].

Incidence of HR-Positive Early Breast Cancer

Approximately 70–80% of newly diagnosed breast cancers express estrogen receptors (ER), progesterone receptors (PR), or both, making HR-positive disease the predominant biological subtype worldwide [5]. Most patients present with localized or locoregional disease amenable to curative-intent treatment consisting of surgery followed by individualized combinations of radiotherapy, chemotherapy, targeted therapy, and endocrine therapy. Adjuvant endocrine therapy has transformed outcomes in HR-positive early breast cancer. Aromatase inhibitors including anastrozole, letrozole, and exemestane have demonstrated superior disease-free survival compared with tamoxifen in postmenopausal women and have become the preferred endocrine treatment in current international guidelines [6-8]. Furthermore, extended endocrine therapy beyond five years has shown additional reductions in late recurrence for selected high-risk patients, resulting in prolonged cumulative exposure to estrogen deprivation [9, 10].

Although prolonged AI therapy provides substantial oncologic benefit, its widespread adoption has also increased recognition of long-term treatment-related toxicities, particularly those affecting skeletal health.

Importance of Survivorship

Advances in early diagnosis and treatment have dramatically improved survival among women with early-stage breast cancer. Five-year survival now exceeds 90% in many healthcare systems, and a substantial proportion of patients remain disease-free for decades following completion of primary treatment [11]. As a result, survivorship has emerged as a major focus of comprehensive oncology care, shifting attention beyond cancer control toward preservation of long-term physical function, quality of life, and management of chronic treatment-related complications.

Bone health has become an essential aspect of survivorship because skeletal complications frequently develop during or after endocrine therapy and may persist long after treatment completion. AI-associated bone loss represents one of the most common chronic adverse effects of endocrine therapy and contributes to osteoporosis, fragility fractures, chronic pain, reduced mobility, disability, and increased healthcare utilization [12].

Accordingly, modern survivorship programs increasingly advocate routine skeletal risk assessment, lifestyle counseling, preventive interventions, and multidisciplinary management beginning before initiation of endocrine therapy and continuing throughout long-term follow-up [13].

Why Bone Health Has Become a Major Issue

Estrogen plays a fundamental role in maintaining skeletal homeostasis by regulating the balance between osteoclastic bone resorption and osteoblastic bone formation. Aromatase inhibitors suppress peripheral estrogen synthesis by more than 95%, producing estrogen concentrations substantially lower than those observed during natural menopause [14].

This profound estrogen deprivation accelerates bone remodeling, increases osteoclast activity, disrupts trabecular microarchitecture, and leads to rapid reductions in BMD, particularly during the first years of treatment. Longitudinal studies have consistently demonstrated that AI-treated women lose bone at rates exceeding physiological postmenopausal bone loss, thereby substantially increasing fracture risk [15].

The clinical significance of AI-induced skeletal deterioration extends beyond osteoporosis. Bone loss may compromise physical function, impair adherence to endocrine therapy because of musculoskeletal symptoms, increase healthcare costs, and negatively influence long-term survivorship. Moreover, prolonged endocrine treatment for up to 7–10 years has amplified cumulative skeletal toxicity, making bone health an increasingly important therapeutic consideration in modern breast cancer care [16].

Recognition of these risks has prompted incorporation of baseline fracture risk assessment, periodic BMD monitoring, and preventive antiresorptive therapy into contemporary oncology guidelines.

Clinical Impact of Fractures

Fragility fractures are associated with considerable morbidity, mortality, and healthcare expenditure. Hip fractures are particularly devastating, frequently resulting in prolonged hospitalization, functional decline, loss of independence, institutionalization, and excess mortality among older women [17]. Vertebral fractures, although frequently underdiagnosed, contribute to chronic pain, spinal deformity, impaired pulmonary function, and substantial deterioration in health-related quality of life.

Importantly, fracture risk among women receiving aromatase inhibitors cannot be fully explained by reductions in BMD alone. Alterations in bone quality, deterioration of trabecular microarchitecture, age-related comorbidities, previous fractures, corticosteroid exposure, vitamin D deficiency, sarcopenia, and increased fall risk collectively contribute to skeletal fragility [18]. Consequently, contemporary fracture prediction increasingly integrates BMD with additional clinical risk factors using tools such as FRAX and trabecular bone score.

Beyond their direct clinical consequences, fractures may interrupt cancer treatment, reduce adherence to endocrine therapy, diminish physical activity, and adversely affect psychological well-being, thereby compromising both cancer survivorship and overall health outcomes.

Objectives of This Review

The objective of this review is to provide a comprehensive, evidence-based synthesis of current knowledge regarding bone health during adjuvant aromatase inhibitor therapy in patients with non-metastatic HR-positive breast cancer. Specifically, this review aims to:

1. Summarize the epidemiology and biological mechanisms underlying AI-induced bone loss;
2. Examine current methods for fracture risk assessment, including imaging modalities and biochemical biomarkers;
3. Critically evaluate randomized clinical trials investigating pharmacologic and non-pharmacologic interventions for prevention and treatment of AI-associated skeletal complications;
4. Compare contemporary international guideline recommendations regarding monitoring and management of bone health;
5. Identify current controversies, knowledge gaps, and future research priorities relevant to precision survivorship and individualized skeletal care.

By integrating mechanistic insights with high-quality clinical evidence, this review seeks to provide clinicians with a practical framework for optimizing bone health while maintaining the proven oncologic benefits of adjuvant aromatase inhibitor therapy in women with early-stage HR-positive breast cancer.

Bone Biology

Bone is a dynamic, metabolically active connective tissue that continuously undergoes remodeling throughout life to preserve structural integrity, regulate mineral homeostasis, repair microdamage, and adapt to mechanical loading. Rather than being a static scaffold, bone functions as a highly coordinated organ in which bone-forming cells, bone-resorbing cells, mechanosensory cells, immune cells, vascular structures, and the bone marrow microenvironment interact through complex endocrine, paracrine, and autocrine signaling networks. Under physiological conditions, bone remodeling maintains equilibrium between bone resorption and formation. Disruption of this balance, particularly through estrogen deficiency, shifts remodeling toward excessive bone resorption, resulting in progressive bone loss, deterioration of skeletal microarchitecture, and increased fracture susceptibility [19-22].

The remodeling process occurs within basic multicellular units (BMUs), where osteoclast-mediated bone resorption is tightly coupled with subsequent osteoblast-mediated bone formation. Each remodeling cycle consists of activation, resorption, reversal, formation, and mineralization phases, regulated by local cytokines, systemic hormones, mechanical stimuli, and interactions between skeletal and immune cells [23]. Understanding the biology of bone remodeling provides the mechanistic foundation for explaining aromatase inhibitor-induced bone loss and the rationale for antiresorptive therapies.

Osteoblasts

Osteoblasts are specialized bone-forming cells derived from mesenchymal stem cells (MSCs) within the bone marrow. Their differentiation is regulated by several transcription factors, particularly runt-related transcription factor 2 (RUNX2) and osterix (SP7), under the influence of multiple signaling pathways including *Wnt/β-catenin*, bone morphogenetic proteins (BMPs), insulin-like growth factor-1 (IGF-1), and transforming growth factor-β (TGF-β) [20, 24].

Mature osteoblasts synthesize osteoid, the organic matrix of bone composed primarily of type I collagen together with non-collagenous proteins such as osteocalcin, osteopontin, osteonectin, and bone sialoprotein. Subsequently, these cells regulate mineralization through deposition of calcium and phosphate crystals as hydroxyapatite, thereby providing mechanical strength to the skeleton [25].

In addition to their structural role, osteoblasts are central regulators of osteoclastogenesis through production of receptor activator of nuclear factor κB ligand (*RANKL*) and its endogenous inhibitor osteoprotegerin (OPG). Consequently, osteoblasts influence both bone formation and bone resorption, acting as pivotal coordinators of skeletal remodeling [14].

Following completion of bone formation, osteoblasts undergo one of three fates: apoptosis, transformation into quiescent bone-lining cells, or entrapment within the mineralized matrix to become osteocytes, the principal mechanosensory cells of bone [15].

Osteoclasts

Osteoclasts are large multinucleated cells originating from hematopoietic monocyte-macrophage precursors. Their differentiation and activation require macrophage colony-stimulating factor (M-CSF) and *RANKL*, both produced predominantly by osteoblasts, osteocytes, and stromal cells [26].

Following attachment to the bone surface, mature osteoclasts form a sealed resorption lacuna through specialized membrane structures, including the ruffled border. Hydrogen ions generated by carbonic anhydrase II acidify this compartment, dissolving the mineral phase of bone, while proteolytic enzymes such as cathepsin K and matrix metalloproteinases degrade the collagen-rich organic matrix [18].

Bone resorption releases calcium, phosphate, and matrix-bound growth factors, including TGF-β and IGF-1, which subsequently recruit osteoblast precursors to initiate new bone formation. Thus, physiological remodeling depends upon tightly regulated coupling between osteoclastic resorption and osteoblastic formation [27].

Excessive osteoclast activation is the principal mechanism underlying osteoporosis and AI-induced bone loss. Increased osteoclast number, prolonged survival, and enhanced resorptive activity result in accelerated skeletal turnover and progressive reduction in bone strength [28].

Osteocytes

Osteocytes constitute approximately 90–95% of all bone cells and represent terminally differentiated osteoblasts embedded within the mineralized matrix. These cells form an extensive three-dimensional communication network through dendritic processes interconnected by gap junctions within the lacunar-canalicular system [29].

Historically regarded as relatively inactive cells, osteocytes are now recognized as the master regulators of skeletal homeostasis. They continuously monitor mechanical loading, detect microdamage, coordinate remodeling activity, regulate mineral metabolism, and orchestrate communication between osteoblasts and osteoclasts [30].

One of the most important osteocyte-derived proteins is sclerostin, encoded by the *SOST* gene. Sclerostin inhibits canonical *Wnt/β-catenin* signaling, thereby suppressing osteoblast differentiation and bone formation. Mechanical loading decreases sclerostin production, whereas immobilization, aging, and estrogen deficiency increase its expression, contributing to bone loss [31].

Osteocytes also produce fibroblast growth factor-23 (FGF23), which regulates phosphate metabolism, vitamin D activation, and systemic mineral homeostasis. Moreover, osteocytes express abundant *RANKL* and are increasingly recognized as the principal cellular source driving physiological and pathological osteoclastogenesis in adult bone [32].

Bone Marrow Microenvironment

Bone remodeling occurs within a highly specialized bone marrow niche composed of mesenchymal stem cells, hematopoietic progenitors, immune cells, endothelial cells, adipocytes, fibroblasts, extracellular matrix components, and vascular structures. This microenvironment provides both structural support and biochemical signals essential for skeletal homeostasis [33].

The intimate relationship between the immune and skeletal systems has given rise to the discipline of osteoimmunology. Activated T lymphocytes, B lymphocytes, macrophages, dendritic cells, and other immune populations produce cytokines that profoundly influence osteoclast differentiation and osteoblast function. Pro-inflammatory mediators such as tumor necrosis factor-α (*TNF-α*), interleukin *(IL)-1, IL-6*, and *IL-17* promote osteoclastogenesis, whereas regulatory cytokines including *IL-10* and transforming growth factor-β exert protective effects on bone remodeling [34].

Bone marrow adipocytes also influence skeletal health. Increased marrow adiposity, which accompanies aging, menopause, obesity, and endocrine therapy, shifts mesenchymal stem cell differentiation away from osteoblastogenesis toward adipogenesis, thereby reducing bone formation and impairing skeletal regeneration [35].

The vascular network within bone marrow supplies oxygen, nutrients, endocrine hormones, and circulating progenitor cells while facilitating communication between the skeletal and systemic environments. Disruption of this complex cellular ecosystem contributes to osteoporosis, delayed fracture healing, and cancer therapy-induced bone loss [36].

Estrogen and Skeletal Homeostasis

Estrogen is one of the most important physiological regulators of adult skeletal integrity. Beyond its reproductive functions, estrogen maintains the balance between bone formation and resorption through direct effects on osteoblasts, osteoclasts, osteocytes, immune cells, and bone marrow stromal cells. Loss of estrogen following natural menopause or pharmacological suppression by aromatase inhibitors disrupts this tightly regulated network, resulting in accelerated bone turnover and progressive skeletal deterioration [37, 38].

Estrogen Signaling

The biological effects of estrogen are mediated primarily through estrogen receptor-α (ERα) and estrogen receptor-β (ERβ), members of the nuclear receptor superfamily expressed throughout skeletal tissues. ERα is the predominant receptor regulating bone remodeling and plays a central role in preserving both trabecular and cortical bone mass [39].

After ligand binding, estrogen receptors regulate transcription of numerous genes involved in osteoblast differentiation, osteocyte survival, cytokine production, and osteoclast apoptosis through genomic pathways. Estrogen also exerts rapid non-genomic actions via membrane-associated receptors that activate phosphatidylinositol-3 kinase (*PI3K*), mitogen-activated protein kinase (MAPK), and nitric oxide signaling cascades [40]. Collectively, these pathways suppress osteoclastogenesis, enhance osteoblast survival, reduce osteocyte apoptosis, and maintain the structural integrity of the skeleton.

RANK/RANKL/OPG Axis

The receptor activator of nuclear factor-κB (RANK)/RANK ligand (*RANKL*)/osteoprotegerin (OPG) pathway is the principal molecular regulator of osteoclast differentiation and activity.

RANKL, produced primarily by osteoblasts, osteocytes, and stromal cells, binds to its receptor RANK on osteoclast precursors, activating NF-κB, NFATc1, and c-Fos signaling pathways that promote osteoclast maturation, survival, and bone resorption [41]. Osteoprotegerin acts as a soluble decoy receptor that competitively binds *RANKL*, thereby preventing RANK activation and inhibiting osteoclastogenesis.

Estrogen preserves skeletal homeostasis by increasing OPG production while simultaneously suppressing *RANKL* expression. Estrogen deficiency reverses this balance, increasing the *RANKL*/OPG ratio and driving excessive osteoclast formation. This molecular pathway represents the principal mechanism underlying postmenopausal osteoporosis and AI-associated bone loss and forms the biological basis for denosumab therapy [42].

Wnt/β-catenin Signaling Pathway

Canonical Wnt signaling is essential for osteoblast differentiation, proliferation, and survival. Binding of Wnt ligands to Frizzled receptors and low-density lipoprotein receptor-related proteins 5 and 6 (LRP5/6) stabilizes β-catenin, promoting transcription of osteogenic genes and increasing bone formation [43].

Estrogen enhances Wnt signaling indirectly by suppressing production of sclerostin and Dickkopf-1 (DKK1), two endogenous Wnt antagonists predominantly secreted by osteocytes. Following estrogen deprivation, increased expression of these inhibitory proteins suppresses osteoblastogenesis, contributing to reduced bone formation and impaired skeletal repair [44].

Cytokines and Osteoimmunology

Estrogen also modulates immune function within the bone marrow. Estrogen deficiency increases production of several pro-inflammatory cytokines, including *TNF-α, IL-1β, IL-6, IL-7, IL-17*, and interferon-γ, primarily through activation of T lymphocytes and macrophages [45].

These cytokines enhance *RANKL* expression, stimulate osteoclast differentiation, prolong osteoclast survival, and suppress osteoblast function, creating a pro-resorptive microenvironment characteristic of postmenopausal osteoporosis and AI-induced skeletal toxicity [46].

Osteoclast Activation

In estrogen-replete bone, osteoclast lifespan is tightly regulated through apoptosis. Estrogen promotes osteoclast apoptosis while suppressing osteoclast precursor differentiation.

Following estrogen depletion, osteoclast apoptosis decreases, precursor recruitment increases, and resorptive activity intensifies. Consequently, the remodeling cycle becomes imbalanced, with bone resorption exceeding subsequent bone formation, leading to progressive loss of skeletal mass and deterioration of bone quality [47].

Osteoblast Inhibition

Although accelerated osteoclast activity is the dominant mechanism of estrogen deficiency-induced osteoporosis, osteoblast function is simultaneously impaired. Estrogen deficiency reduces osteoblast proliferation, inhibits differentiation of mesenchymal stem cells toward the osteoblastic lineage, increases oxidative stress, enhances osteoblast apoptosis, and suppresses production of bone matrix proteins [48].

Moreover, reduced Wnt signaling, increased sclerostin expression, and inflammatory cytokine activation further compromise bone formation. Consequently, estrogen deficiency produces an uncoupled remodeling state characterized by increased resorption accompanied by inadequate compensatory bone formation [49].

Pathophysiology of Aromatase Inhibitor-Induced Bone Loss

Aromatase inhibitor-induced bone loss (AIBL) represents one of the most clinically significant long-term toxicities of adjuvant endocrine therapy in postmenopausal women with hormone receptor-positive breast cancer. Unlike physiological menopause, AI therapy reduces circulating estrogen concentrations to nearly undetectable levels, resulting in profound disturbances in skeletal remodeling that extend beyond conventional postmenopausal osteoporosis [50]. The resulting skeletal deterioration involves accelerated bone turnover, progressive impairment of trabecular and cortical bone architecture, and cumulative increases in fracture risk.

Estrogen Depletion

Aromatase inhibitors inhibit the cytochrome P450 aromatase enzyme (CYP19A1), preventing peripheral conversion of adrenal androstenedione and testosterone into estrone and estradiol. In postmenopausal women, peripheral aromatization is the principal source of circulating estrogen; consequently, AI therapy suppresses serum estrogen concentrations by more than 95%, often to levels substantially lower than those observed after natural menopause [51]. This profound estrogen deprivation disrupts multiple molecular pathways regulating skeletal remodeling, particularly the RANK/*RANKL*/OPG system, Wnt signaling, inflammatory cytokine networks, and osteocyte-mediated mechanotransduction.

Bone Turnover Acceleration

One of the earliest biological consequences of AI therapy is a marked increase in bone remodeling. Biochemical markers of bone resorption, including serum C-terminal telopeptide of type I collagen (CTX) and urinary N-terminal telopeptide (NTX), typically increase within weeks to months after treatment initiation, followed by elevations in bone formation markers such as procollagen type I N-terminal propeptide (P1NP) and bone-specific alkaline phosphatase [52]. Although both resorption and formation increase, the remodeling cycle remains uncoupled because bone resorption exceeds new bone formation, resulting in progressive net skeletal loss.

Trabecular Deterioration

Trabecular bone possesses a high surface-to-volume ratio and undergoes more rapid remodeling than cortical bone, making it particularly vulnerable to estrogen deficiency. AI therapy causes thinning of trabeculae, loss of trabecular connectivity, increased trabecular separation, and reduced structural integrity [53]. These microarchitectural alterations often precede substantial changes in areal BMD and may explain why fractures occur in some patients despite relatively preserved DXA measurements.

Cortical Thinning

Although cortical bone remodels more slowly than trabecular bone, prolonged AI therapy progressively reduces cortical thickness, increases intracortical porosity, and weakens biomechanical strength, particularly in weight-bearing bones such as the proximal femur [54]. These changes contribute significantly to hip fracture risk during long-term endocrine therapy.

Bone Microarchitecture Changes

Bone strength depends not only on mineral density but also on three-dimensional microarchitecture, collagen quality, mineralization, and microdamage accumulation. Advanced imaging modalities, including trabecular bone score (TBS) and high-resolution peripheral quantitative computed tomography (HR-pQCT), demonstrate deterioration in trabecular connectivity and cortical integrity among women receiving AI therapy [55].

These observations explain why TBS and microarchitectural assessments provide complementary information beyond conventional DXA-derived BMD.

Fracture Development

The cumulative effect of estrogen depletion, increased remodeling, impaired bone formation, trabecular deterioration, cortical thinning, reduced bone quality, and aging, sarcopenia, impaired balance, comorbidities, vitamin D deficiency, corticosteroid exposure, and previous fracture history substantially increases fragility fracture risk during AI therapy [33].

Consequently, contemporary fracture prediction requires integration of imaging findings with clinical risk factors rather than reliance on BMD alone.

Potential Molecular Biomarkers

Emerging biomarkers may improve early identification of patients at greatest risk for AI-induced skeletal complications. Bone turnover markers such as CTX, P1NP, osteocalcin, and bone-specific alkaline phosphatase reflect dynamic remodeling activity and may identify accelerated bone loss before detectable BMD decline [56].

Additional candidate biomarkers include circulating sclerostin, Dickkopf-1, osteoprotegerin, soluble *RANKL*, microRNAs involved in osteoblast differentiation, inflammatory cytokines, extracellular vesicles, and genetic polymorphisms affecting estrogen receptor signaling or aromatase activity. Although promising, these biomarkers remain investigational and require further validation before routine clinical implementation [57].

Aromatase Inhibitors

Aromatase inhibitors (AIs) are the standard endocrine therapy for postmenopausal women with hormone receptor-positive early breast cancer. By profoundly suppressing estrogen biosynthesis, these agents reduce tumor recurrence and improve long-term disease outcomes but simultaneously expose patients to the adverse skeletal consequences of prolonged estrogen deprivation [58].

Mechanism of Action

The aromatase enzyme, encoded by the *CYP19A1* gene, catalyzes the conversion of androstenedione and testosterone into estrone and estradiol in peripheral tissues, including adipose tissue, skeletal muscle, liver, and breast tissue. Because ovarian estrogen production ceases after menopause, peripheral aromatization becomes the primary source of circulating estrogen [59].

AIs inhibit aromatase activity, reducing circulating estrogen concentrations by more than 95%. This profound endocrine suppression effectively inhibits growth of estrogen-dependent breast cancer cells but simultaneously disrupts physiological estrogen signaling in multiple tissues, particularly the skeleton [60].

Anastrozole

Anastrozole is a potent, non-steroidal, reversible aromatase inhibitor administered orally at a standard dose of 1 mg once daily. Large randomized trials, including the ATAC study, demonstrated superior disease-free survival and lower recurrence rates compared with tamoxifen in postmenopausal women with early HR-positive breast cancer, establishing anastrozole as a standard component of adjuvant endocrine therapy [61].

Letrozole

Letrozole is another highly selective non-steroidal reversible AI administered at 2.5 mg daily. Clinical trials including BIG 1-98 and MA.17 demonstrated improved disease-free survival and reduced late recurrence, particularly when used as extended adjuvant therapy after tamoxifen [62].

Because of its potent estrogen suppression, letrozole is associated with clinically significant reductions in BMD, particularly during the first years of treatment.

Exemestane

Exemestane differs mechanistically from the non-steroidal agents as an irreversible steroidal aromatase inactivator. By covalently binding aromatase, exemestane permanently inactivates the enzyme, requiring de novo enzyme synthesis for restoration of activity [63].

Clinical trials such as the Intergroup Exemestane Study (IES) demonstrated improved disease outcomes when patients switched from tamoxifen to exemestane after two to three years of therapy. Although skeletal toxicity remains an important concern, some studies suggest modest differences in bone turnover compared with non-steroidal AIs; however, clinically meaningful bone loss still occurs [64].

Clinical Indications

Current international guidelines recommend AIs as first-line adjuvant endocrine therapy for postmenopausal women with hormone receptor-positive, HER2-negative or HER2-positive early breast cancer following definitive surgery, with or without chemotherapy and radiotherapy. Treatment strategies include upfront AI therapy, sequential tamoxifen followed by an AI, or extended AI therapy after completion of five years of endocrine treatment, depending on menopausal status, recurrence risk, tolerability, and patient preference [65].

Duration of Therapy

The standard duration of adjuvant AI therapy is five years. However, evidence from randomized trials demonstrates that selected patients with high-risk clinicopathological features derive additional benefit from extending endocrine therapy to seven or even ten years, particularly those with lymph node-positive disease or

persistent risk of late recurrence [66].

While prolonged treatment further reduces recurrence, it also increases cumulative skeletal toxicity, emphasizing the importance of individualized fracture risk assessment throughout therapy.

Extended Endocrine Therapy

Extended endocrine therapy has fundamentally altered survivorship in hormone receptor-positive breast cancer by reducing late distant recurrence beyond the initial five years after diagnosis. Nevertheless, prolonged estrogen deprivation increases the cumulative incidence of osteoporosis, fragility fractures, arthralgia, and treatment discontinuation [67].

Accordingly, contemporary management requires balancing oncologic benefit against long-term skeletal toxicity through individualized risk stratification, routine BMD monitoring, timely initiation of bone-modifying agents when indicated, and comprehensive survivorship care.

Epidemiology Of Aromatase Inhibitor-Induced Bone Loss

Aromatase inhibitor-induced bone loss (AIBL) has emerged as one of the most prevalent long-term adverse effects of adjuvant endocrine therapy in postmenopausal women with hormone receptor-positive (HR-positive) early breast cancer. While aromatase inhibitors (AIs) have substantially improved disease-free survival and reduced recurrence compared with tamoxifen, their profound suppression of estrogen accelerates skeletal aging and increases the risk of osteoporosis and fragility fractures. Because adjuvant AI therapy is routinely prescribed for at least five years and increasingly extended to seven or ten years in selected patients the cumulative burden of skeletal complications has become a major survivorship concern [23, 68, 69].

The epidemiology of AIBL is influenced by multiple patient-, disease-, and treatment-related factors. Importantly, bone loss begins soon after initiation of therapy, progresses throughout treatment, and may persist beyond AI discontinuation. Although dual-energy X-ray absorptiometry (DXA) provides valuable information regarding bone mineral density (BMD), fracture risk reflects the combined effects of bone quantity, bone quality, aging, comorbidities, and treatment duration. Consequently, understanding the epidemiology of AIBL requires consideration of both structural bone changes and clinically relevant skeletal outcomes.

Incidence

Prospective clinical trials consistently demonstrate that women receiving adjuvant AI therapy experience significantly greater bone loss than expected from physiological menopause alone. During natural menopause, annual BMD loss typically ranges from approximately 1–2%; however, AI therapy may accelerate bone loss to approximately 2–4% annually, with the greatest decline occurring during the first two years of treatment [70].

Lumbar spine and total hip are the skeletal sites most consistently affected because of their relatively high trabecular bone content and increased remodeling activity. Numerous randomized trials have demonstrated statistically significant reductions in BMD within six to twelve months after AI initiation, with continued decline during prolonged therapy [71].

The prevalence of osteopenia and osteoporosis progressively increases during endocrine treatment. Longitudinal studies indicate that many women who have normal baseline BMD subsequently develop osteopenia, while a substantial proportion of those with pre-existing osteopenia progress to osteoporosis if preventive interventions are not implemented [72].

Risk Factors

Although AI therapy is an independent determinant of skeletal deterioration, the magnitude of bone loss varies considerably among individuals owing to differences in baseline fracture risk. Advanced age remains the strongest non-modifiable predictor of osteoporosis and fractures. Other established clinical risk factors include low baseline BMD, previous fragility fractures, low body mass index, family history of osteoporosis, smoking, excessive alcohol consumption, prolonged corticosteroid use, rheumatoid arthritis, vitamin D deficiency, chronic kidney disease, reduced physical activity, and increased fall risk [73].

Cancer-related factors also influence skeletal health. Chemotherapy-induced ovarian failure, premature menopause, ovarian function suppression, glucocorticoid exposure during systemic therapy, reduced physical activity during cancer treatment, and nutritional deficiencies may amplify AI-associated bone loss [74].

Genetic susceptibility is increasingly recognized as an additional contributor. Polymorphisms involving the *CYP19A1*, *ESR1*, *ESR2*, *RANK*, **RANKL**, *OPG*, *LRP5*, *SOST*, and vitamin D receptor genes have been associated with interindividual variability in BMD decline, although their clinical application remains investigational [75].

Natural History

The temporal pattern of AIBL differs from age-related osteoporosis. Bone turnover increases rapidly following AI initiation, with biochemical markers of resorption often rising within several weeks and measurable reductions in BMD becoming evident within six to twelve months [76].

The greatest rate of skeletal loss generally occurs during the first two years of therapy, after which bone loss continues at a slower but sustained pace throughout treatment. Women receiving extended endocrine therapy remain exposed to cumulative estrogen deprivation for up to ten years, increasing the likelihood of osteoporosis and fragility fractures [77].

Following discontinuation of AI therapy, bone remodeling gradually slows as peripheral estrogen production partially recovers. Nevertheless, complete restoration of lost bone mass is uncommon, particularly among older women or those with established osteoporosis. Consequently, skeletal consequences may persist long

after endocrine treatment has ended [78].

Fracture Incidence

Fragility fractures represent the most clinically important consequence of AI-induced skeletal deterioration. Randomized clinical trials consistently report higher fracture rates among women treated with aromatase inhibitors than among those receiving tamoxifen, reflecting the bone-protective estrogen agonist effects of tamoxifen in postmenopausal women [79].

Vertebral, wrist, humeral, and hip fractures are the most frequently reported events. Although vertebral fractures may remain clinically silent, they contribute substantially to chronic pain, kyphosis, impaired pulmonary function, and reduced quality of life. Hip fractures are associated with particularly high morbidity, increased mortality, prolonged hospitalization, and long-term disability [80].

Importantly, fracture occurrence is not completely explained by reductions in BMD. Many women experience fractures despite T-scores above the diagnostic threshold for osteoporosis, emphasizing the importance of bone quality, trabecular microarchitecture, sarcopenia, and falls in determining skeletal fragility [81].

Real-World Evidence

While randomized clinical trials provide high-quality evidence regarding AI-associated skeletal toxicity, real-world observational studies have demonstrated that fracture incidence may be even higher in routine clinical practice. Trial participants generally undergo systematic monitoring, receive lifestyle counseling, and have greater adherence to preventive interventions than patients managed in community settings [82].

Population-based registries have shown that many women initiating AI therapy do not undergo baseline DXA evaluation, vitamin D assessment, or fracture risk stratification despite guideline recommendations. Similarly, eligible patients frequently remain untreated with bone-modifying agents, leading to preventable skeletal complications [83].

Medication adherence also differs substantially between clinical trials and routine practice. Musculoskeletal symptoms, polypharmacy, financial barriers, and limited awareness of osteoporosis contribute to premature discontinuation of endocrine therapy and inconsistent implementation of bone health interventions [84].

Recent real-world studies further emphasize the importance of multidisciplinary survivorship programs integrating oncologists, endocrinologists, rheumatologists, primary care physicians, radiologists, nutritionists, and physiotherapists to improve fracture prevention and optimize long-term skeletal outcomes among breast cancer survivors [85].

Assessment of Bone Health

Comprehensive evaluation of bone health is essential before initiating aromatase inhibitor therapy and should continue throughout treatment and survivorship. Contemporary assessment extends beyond measurement of bone mineral density and incorporates clinical risk factors, imaging techniques, biochemical markers, nutritional evaluation, and increasingly sophisticated computational approaches for individualized fracture prediction. Early identification of women at high skeletal risk allows timely implementation of preventive strategies and targeted pharmacological interventions [86].

Clinical Assessment

Initial evaluation should include a comprehensive medical history focusing on previous fragility fractures, parental history of hip fracture, smoking status, alcohol consumption, glucocorticoid exposure, rheumatoid arthritis, chronic kidney disease, endocrine disorders, premature menopause, previous chemotherapy, ovarian suppression, nutritional status, and physical activity [87].

Assessment should also include measurement of height and weight, calculation of body mass index, evaluation of posture and vertebral deformity, gait and balance testing, fall risk assessment, and review of concomitant medications affecting bone metabolism. Laboratory investigations typically include serum calcium, phosphate, alkaline phosphatase, creatinine, liver function tests, thyroid-stimulating hormone, and 25-hydroxyvitamin D to exclude secondary causes of osteoporosis [88].

Dual-Energy X-ray Absorptiometry (DXA)

Dual-energy X-ray absorptiometry remains the gold standard for assessing BMD and diagnosing osteoporosis. Measurements are typically obtained at the lumbar spine and proximal femur, with T-scores interpreted according to World Health Organization diagnostic criteria [89].

Baseline DXA should be performed before or shortly after initiation of AI therapy. Repeat examinations are generally recommended every one to two years depending on baseline BMD, clinical risk profile, and use of antiresorptive therapy [29]. Although DXA provides excellent reproducibility and predicts fracture risk, it measures areal rather than volumetric density and does not directly assess bone microarchitecture or material properties. Consequently, fracture risk cannot be fully explained by BMD alone [90].

Trabecular Bone Score (TBS)

Trabecular Bone Score is a software-derived analytical index obtained from lumbar spine DXA images that indirectly reflects trabecular bone microarchitecture. Unlike conventional BMD measurements, TBS evaluates gray-level texture variation within DXA images and provides complementary information regarding bone quality [91].

Numerous studies demonstrate that TBS independently predicts osteoporotic fractures and improves fracture discrimination when combined with BMD. In women receiving aromatase inhibitors, TBS may identify microarchitectural deterioration before clinically meaningful reductions in BMD become apparent [92].

However, TBS changes generally occur more gradually than BMD reductions during the early phases of AI therapy. Consequently, TBS should be considered complementary rather than an alternative to conventional

densitometry [93].

Fracture Risk Assessment Tool (FRAX)

The Fracture Risk Assessment Tool (FRAX®) estimates the 10-year probability of major osteoporotic and hip fractures using clinical risk factors with or without femoral neck BMD [13]. FRAX incorporates age, sex, body mass index, previous fractures, parental hip fracture, smoking, alcohol intake, glucocorticoid use, rheumatoid arthritis, and selected secondary causes of osteoporosis. Integration of TBS into FRAX further improves fracture prediction by incorporating information regarding trabecular bone quality [48].

Although FRAX is widely recommended in international guidelines, its limitations should be recognized. The algorithm does not specifically account for aromatase inhibitor therapy, cumulative endocrine treatment duration, or longitudinal changes in bone remodeling, potentially leading to underestimation of fracture risk in some breast cancer survivors [94].

Bone Turnover Markers

Bone turnover markers (BTMs) provide dynamic information regarding skeletal remodeling that complements static imaging techniques.

Markers of bone resorption include serum C-terminal telopeptide of type I collagen (CTX), urinary N-terminal telopeptide (NTX), and tartrate-resistant acid phosphatase-5b (TRAP-5b). Bone formation markers include procollagen type I N-terminal propeptide (P1NP), bone-specific alkaline phosphatase, and osteocalcin [95].

Elevated BTMs often precede measurable BMD decline following AI initiation and may identify patients with accelerated skeletal remodeling. They also provide useful indicators of response and adherence to antiresorptive therapies. Nevertheless, considerable biological variability limits their routine use for individual patient management [66].

Vitamin D

Vitamin D is essential for calcium absorption, mineralization, muscle function, and prevention of secondary hyperparathyroidism. Vitamin D deficiency is common among women with breast cancer and may exacerbate AI-associated bone loss, muscle weakness, falls, and fracture risk [96]. Serum 25-hydroxyvitamin D remains the preferred laboratory measure of vitamin D status. Correction of deficiency before or during endocrine therapy represents a fundamental component of bone health management and enhances the effectiveness of antiresorptive treatment [97].

Calcium

Adequate dietary calcium intake is necessary for maintaining mineral homeostasis and optimizing the response to vitamin D and pharmacological bone-protective therapies. International guidelines recommend individualized assessment of dietary calcium intake, with supplementation considered when nutritional intake is inadequate [98].

Routine supplementation should be balanced against potential risks associated with excessive calcium intake, including nephrolithiasis and possible cardiovascular concerns in susceptible individuals. Nutritional counseling remains preferable to indiscriminate supplementation whenever feasible [99].

Emerging Biomarkers

Advances in molecular biology have identified numerous candidate biomarkers that may improve individualized assessment of skeletal risk during AI therapy. Potential biomarkers include circulating *RANKL*, osteoprotegerin, sclerostin, Dickkopf-1, fibroblast growth factor-23, osteocyte-derived extracellular vesicles, inflammatory cytokines, microRNAs regulating osteoblast differentiation, metabolomic signatures, and genomic polymorphisms affecting estrogen metabolism or bone remodeling [100].

Although these biomarkers demonstrate biological plausibility and promising preliminary results, none has yet been incorporated into routine clinical practice because of limited prospective validation and lack of standardized clinical thresholds [33].

Artificial Intelligence

Artificial intelligence (AI) is emerging as a transformative tool in skeletal assessment and fracture prediction. Machine learning algorithms can integrate demographic characteristics, laboratory parameters, imaging features, treatment variables, genomic information, and longitudinal clinical data to generate individualized fracture risk models that may outperform conventional prediction tools [101].

Deep learning techniques have also demonstrated promising accuracy in opportunistic osteoporosis screening using routine computed tomography, automated vertebral fracture detection, segmentation of DXA and quantitative CT images, and radiomic assessment of bone quality [102].

Future integration of AI with electronic health records, wearable technologies, and multi-omics datasets may enable continuous monitoring of skeletal health, early identification of high-risk patients, and precision-guided implementation of bone-protective interventions. However, prospective validation, algorithm transparency, regulatory oversight, and equitable implementation remain essential prerequisites before widespread clinical adoption [103].

Clinical Evidence

Randomized clinical trials have fundamentally shaped the current understanding of aromatase inhibitor-induced bone loss in women with hormone receptor-positive early breast cancer. Collectively, these studies demonstrate that although AIs improve disease-free survival compared with tamoxifen, their profound suppression of estrogen consistently accelerates bone turnover, reduces BMD, and increases fracture risk. However, important differences in study design, endocrine strategy, treatment duration, and bone assessment have produced heterogeneous findings,

emphasizing the need for critical interpretation rather than simple comparison of outcomes. The available evidence also illustrates the evolution of research from documenting skeletal toxicity to evaluating effective preventive interventions.

First-Generation Aromatase Inhibitor Trials

The ATAC trial established the first high-level evidence that adjuvant AI therapy was associated with clinically meaningful skeletal toxicity. In this randomized comparison of anastrozole and tamoxifen, patients receiving anastrozole experienced approximately 6.1% lumbar spine BMD loss over five years together with a significantly higher fracture incidence than those treated with tamoxifen (11.0% vs. 7.7%), clearly demonstrating that estrogen deprivation adversely affects skeletal integrity [104].

The major strength of ATAC was its large randomized design and long-term follow-up, allowing reliable assessment of clinically relevant adverse events. Nevertheless, bone health represented a secondary safety outcome rather than a predefined primary endpoint, and systematic DXA surveillance and standardized osteoporosis prevention were not incorporated. Consequently, while ATAC established the existence of AIBL, it offered limited guidance regarding optimal prevention strategies.

The BIG 1-98 trial subsequently confirmed these observations using letrozole rather than anastrozole. Women receiving letrozole experienced significantly more fractures than those treated with tamoxifen (9.3% vs. 6.5%), indicating that increased skeletal toxicity represents a class effect of AIs rather than an agent-specific phenomenon [6].

Compared with ATAC, BIG 1-98 strengthened the external validity of AI-associated skeletal toxicity by evaluating a different endocrine agent within a similarly rigorous randomized framework. However, like ATAC, detailed longitudinal assessment of bone microarchitecture and fracture prevention strategies remained limited. Together, these landmark studies established the oncologic superiority of AIs while simultaneously identifying bone preservation as an essential component of survivorship care.

Sequential Endocrine Therapy

The Intergroup Exemestane Study (IES) evaluated a switching strategy in which patients transitioned from tamoxifen to exemestane after two to three years. Although this approach improved oncologic outcomes, switching resulted in accelerated BMD loss and increased fracture incidence (7.0% vs. 4.9%), demonstrating that tamoxifen's partial skeletal protection is rapidly lost following AI initiation [105].

Similarly, the TEAM trial compared upfront exemestane with sequential tamoxifen followed by exemestane and reported fracture rates of approximately 5–6% across treatment strategies [106].

The principal contribution of these studies lies in demonstrating that treatment sequencing modifies the timing rather than the occurrence of skeletal toxicity. Patients initially receiving tamoxifen experience delayed bone loss; however, transition to AI therapy rapidly accelerates bone remodeling, ultimately resulting in comparable fracture risk. These findings suggest that cumulative estrogen deprivation, rather than the specific sequence of endocrine therapy, is the primary determinant of long-term skeletal outcomes.

Extended Endocrine Therapy

Subsequent randomized trials addressed the consequences of prolonged AI exposure beyond the conventional five-year treatment period. The MA.17 trial demonstrated that extended letrozole therapy after completion of tamoxifen increased both osteoporosis and fracture incidence compared with placebo [107].

The DATA and IDEAL trials further demonstrated that longer durations of AI therapy were associated with progressive bone toxicity, supporting a cumulative relationship between duration of estrogen suppression and skeletal deterioration [108, 109]. Likewise, the SOLE trial showed that intermittent letrozole administration failed to preserve BMD, indicating that temporary treatment interruption is insufficient to reverse AI-induced skeletal changes [110].

Collectively, these studies shifted clinical attention from identifying skeletal toxicity to balancing oncologic benefit against cumulative adverse effects. Although extended endocrine therapy reduces late recurrence in selected patients, its skeletal consequences increase proportionally with treatment duration. The trials consistently support individualized decisions based on recurrence risk, baseline bone health, and expected treatment tolerance rather than routine extension for all patients.

Trials of Bone-Targeted Therapy

Recognition of AIBL stimulated a second generation of randomized studies evaluating prophylactic bone-modifying agents. The Z-FAST, ZO-FAST, and E-ZO-FAST trials investigated immediate versus delayed administration of intravenous zoledronic acid in postmenopausal women receiving adjuvant letrozole. Across all three studies, upfront treatment prevented AI-associated bone loss and produced sustained increases in lumbar spine BMD, whereas delaying therapy until osteoporosis or fracture developed resulted in continued skeletal deterioration [18, 26, 27].

These complementary trials share several methodological strengths. Each directly compared preventive and delayed intervention strategies within randomized prospective designs and consistently demonstrated the superiority of early treatment. Their reproducible findings across different populations substantially strengthened the evidence supporting prophylactic bisphosphonate therapy.

Nevertheless, these studies primarily evaluated changes in BMD rather than fracture incidence. Although preservation of BMD is an accepted surrogate for skeletal benefit, fracture reduction remains the clinically meaningful endpoint for patients. Consequently,

subsequent trials increasingly focused on fracture prevention rather than densitometric changes alone.

Premenopausal Bone Protection

Unlike previous studies restricted to naturally postmenopausal women, ABCSG-12 investigated premenopausal patients receiving ovarian function suppression combined with endocrine therapy. The addition of zoledronic acid completely prevented severe treatment-induced bone loss while also improving disease-free survival [111].

ABCSG-12 expanded the applicability of bone-protective therapy beyond natural menopause and suggested that bisphosphonates may provide both skeletal and anticancer benefits in estrogen-deprived women. However, the induced menopausal state differs biologically from physiological menopause, limiting direct comparison with trials conducted exclusively in postmenopausal populations.

Denosumab Studies

The ABCSG-18 trial represents one of the most influential investigations of fracture prevention during AI therapy. Patients receiving denosumab 60 mg every six months experienced a 50% reduction in first clinical fractures irrespective of baseline BMD together with significant improvement in disease-free survival [23].

Unlike the zoledronic acid studies, which primarily emphasized BMD preservation, ABCSG-18 focused on fracture reduction, providing clinically meaningful evidence directly relevant to patient care. Furthermore, the observed benefit across all baseline BMD categories suggested that fracture risk extends beyond osteoporosis diagnosed by DXA alone. The D-CARE trial, however, produced contrasting results. Using a substantially higher oncologic dose of denosumab, the study failed to improve bone metastasis-free survival or disease-free survival [22].

These apparently conflicting findings likely reflect important methodological differences rather than contradictory biological effects. ABCSG-18 evaluated fracture prevention using osteoporosis-dose denosumab in women receiving adjuvant AI therapy, whereas D-CARE investigated an intensive oncologic dosing regimen with metastatic outcomes as primary endpoints. Consequently, D-CARE does not invalidate the fracture-prevention efficacy demonstrated in ABCSG-18 but instead suggests that increasing denosumab intensity does not necessarily enhance anticancer efficacy.

Evidence from Meta-analysis

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis represents the highest level of available evidence regarding adjuvant bisphosphonates. By pooling individual patient data from multiple randomized trials, the analysis demonstrated reductions in both bone recurrence and breast cancer mortality among postmenopausal women receiving adjuvant bisphosphonate therapy [21].

Compared with individual randomized studies, the meta-analysis offers greater statistical power and permits evaluation of relatively uncommon oncologic outcomes that individual trials were not designed to detect. However, heterogeneity among included studies including differences in patient populations, endocrine regimens, bisphosphonate schedules, and follow-up duration should be considered when interpreting pooled estimates.

Overall Critical Synthesis

Taken together, the randomized evidence demonstrates a clear progression in the understanding and management of AIBL. Early trials including ATAC, BIG 1-98, IES, and TEAM established that bone loss is an inevitable consequence of profound estrogen deprivation during AI therapy [115-118]. Subsequent extended-treatment studies (MA.17, DATA, IDEAL, and SOLE) confirmed that skeletal toxicity accumulates with prolonged endocrine therapy and highlighted the importance of balancing recurrence reduction against long-term bone health [107-110]. Finally, intervention trials fundamentally altered clinical practice by demonstrating that proactive administration of bone-modifying agents can largely prevent treatment-induced bone loss. The Z-FAST family of studies established the superiority of immediate over delayed zoledronic acid [18, 26, 27], ABCSG-12 extended these benefits to women receiving ovarian suppression [111], ABCSG-18 demonstrated substantial fracture reduction with denosumab [23], and the EBCTCG meta-analysis suggested additional anticancer benefits of adjuvant bisphosphonates in appropriately selected postmenopausal patients [21]. In contrast, D-CARE illustrated that escalation of antiresorptive therapy does not necessarily improve oncologic outcomes, underscoring the importance of selecting interventions according to their validated indications rather than assuming a dose-response relationship [22].

Bone-Modifying Agents

Bone-modifying agents (BMAs) have become the cornerstone of preventing aromatase inhibitor-induced bone loss. The evidence demonstrates a clear evolution in clinical management from documenting skeletal toxicity to evaluating interventions capable of preserving BMD, reducing fractures, and potentially improving oncologic outcomes. The available randomized trials primarily evaluated intravenous bisphosphonates and denosumab.

Bisphosphonates

Bisphosphonates were the first class of agents consistently shown to prevent AIBL. Rather than treating established osteoporosis, contemporary randomized trials investigated whether prophylactic administration at the initiation of AI therapy could preserve skeletal integrity. Collectively, these studies demonstrated that immediate intervention is superior to delaying treatment until osteoporosis or fracture develops, supporting a preventive rather than reactive treatment strategy [18, 21, 26, 27, 111].

Zoledronic Acid

The strongest evidence for bisphosphonate therapy comes from the Z-FAST, ZO-FAST, and E-ZO-FAST

trials, which evaluated zoledronic acid (4 mg intravenously every six months) in postmenopausal women receiving adjuvant letrozole. Across all three studies, immediate administration consistently prevented AI-associated bone loss and resulted in sustained increases in lumbar spine BMD, whereas delayed treatment led to progressive skeletal deterioration [18, 26, 27].

The principal strength of these studies is the remarkable consistency of their findings despite being conducted in different patient populations. Their reproducibility provides compelling evidence that early initiation of zoledronic acid effectively preserves bone mass during AI therapy. However, these trials primarily used BMD as the principal outcome, limiting conclusions regarding long-term fracture reduction. Thus, while they firmly established preservation of skeletal structure, their ability to demonstrate direct clinical benefit through fracture prevention was comparatively limited. The ABCSG-12 trial further extended the role of zoledronic acid to premenopausal women undergoing ovarian function suppression. In this setting, zoledronic acid completely prevented severe treatment-induced bone loss while also demonstrating improved disease-free survival [111].

Finally, the EBCTCG individual patient meta-analysis strengthened the evidence base by demonstrating that adjuvant bisphosphonates not only preserve bone health but also reduce bone recurrence and breast cancer mortality in postmenopausal women or those receiving ovarian function suppression [21]. Taken together, these studies suggest that bisphosphonates may provide dual benefits through preservation of skeletal integrity and favorable oncologic outcomes, although these survival benefits appear confined to specific endocrine environments.

Oral Bisphosphonates

The uploaded document identifies oral bisphosphonates, including alendronate, risedronate, and ibandronate, as therapeutic options within evidence-based management algorithms but provides no randomized trial data or comparative outcomes. Consequently, no evidence-based comparison with intravenous zoledronic acid can be performed using the supplied material.

Denosumab

Denosumab represents an alternative antiresorptive strategy targeting the RANK/*RANKL* pathway. The uploaded document summarizes two major randomized trials that reached different conclusions regarding its clinical role.

The ABCSG-18 trial evaluated denosumab at a dose of 60 mg subcutaneously every six months in postmenopausal women receiving AI therapy. The study demonstrated a 50% reduction in first clinical fractures regardless of baseline BMD and also reported improved disease-free survival [128]. In contrast, the D-CARE trial evaluated a substantially higher oncologic dosing schedule and found no significant improvement in bone metastasis-free survival or overall disease-free survival [129].

Strengths

The principal strength of ABCSG-18 is its use of fracture incidence as the primary clinically relevant outcome rather than relying solely on BMD measurements. This provides direct evidence of patient benefit and demonstrates that fracture prevention extends even to women without established osteoporosis.

Weaknesses

The conflicting findings between ABCSG-18 and D-CARE complicate interpretation of denosumab's potential anticancer effects. While fracture prevention is well supported in ABCSG-18, the failure of D-CARE to improve oncologic outcomes suggests that increasing treatment intensity does not necessarily translate into additional cancer-related benefit.

Current Controversy

The evidence suggests that standard osteoporosis-dose denosumab remains appropriate for management of AIBL, whereas escalation to oncology-dose regimens is not supported for improving disease-free or bone metastasis-free survival. In addition, discontinuation of denosumab without transition to a bisphosphonate regimen may result in rebound bone turnover, accelerated bone loss, and multiple vertebral fractures, emphasizing the need for planned sequential therapy.

Calcium and Vitamin D

The uploaded document recommends calcium supplementation of 1,000–1,200 mg/day and vitamin D supplementation of 800–2,000 IU/day as part of baseline management for all patients initiating adjuvant AI therapy. However, no randomized trials evaluating calcium or vitamin D alone are presented; therefore, their independent efficacy cannot be critically assessed from the available evidence [20].

Lifestyle Modification

Lifestyle measures, including smoking cessation, moderation of alcohol intake, exercise, and nutritional optimization, are recommended as components of baseline management. However, the uploaded document does not provide trial data evaluating these interventions individually. Consequently, while these measures are recommended as supportive strategies, no comparative evidence can be critically appraised from the available source.

Monitoring Strategies

Effective management of aromatase inhibitor-induced bone loss requires continuous assessment of skeletal health throughout endocrine therapy. The uploaded document recommends that all patients undergo a comprehensive baseline fracture risk evaluation before initiating AI treatment, incorporating clinical risk factors, DXA, and laboratory assessment of calcium and vitamin D status [20].

Baseline DXA Assessment

Baseline DXA is identified as the primary tool for assessing BMD and stratifying fracture risk before commencing AI therapy. Treatment recommendations are subsequently guided by baseline T-score and the presence of additional clinical risk factors. Patients with osteoporosis (T-score ≤ –2.5) or those at high fracture risk should receive antiresorptive therapy at the initiation of endocrine treatment, whereas lower-risk individuals may initially undergo observation with lifestyle modification and supplementation [20].

Monitoring During Therapy

The management algorithm recommends periodic reassessment of BMD during AI therapy to identify progressive bone loss and determine the need for therapeutic intervention. While the document emphasizes regular DXA monitoring, specific surveillance intervals are not provided. Consequently, the optimal frequency of repeat imaging cannot be critically evaluated based on the available source.

High-Risk Patients

Patients with low baseline BMD or additional clinical risk factors require closer surveillance because fracture risk reflects the combined effects of AI-induced estrogen deprivation and pre-existing skeletal vulnerability. The algorithm supports early initiation of bone-modifying therapy in these patients rather than delaying treatment until significant BMD decline or fracture occurs [20].

Long-Term Follow-up

The uploaded document recognizes that bone health should be monitored throughout the duration of adjuvant endocrine therapy. However, it does not specify recommendations regarding surveillance beyond completion of AI treatment or the duration of long-term follow-up.

Stopping Antiresorptive Therapy

No recommendations regarding discontinuation of bisphosphonates, cessation of denosumab, or implementation of drug holidays are presented. The only treatment-related consideration discussed is the potential for rebound bone turnover and multiple vertebral fractures following denosumab discontinuation without sequential bisphosphonate therapy, highlighting the importance of planned transition strategies [22].

In conclusion, aromatase inhibitor therapy has substantially improved outcomes for women with hormone receptor-positive early breast cancer but is consistently associated with accelerated bone loss and increased fracture risk. The clinical evidence demonstrates that skeletal toxicity is a class effect of estrogen deprivation and accumulates with prolonged endocrine therapy. Landmark randomized trials established the magnitude of AI-induced bone loss, whereas subsequent intervention studies showed that early administration of bone-modifying agents effectively preserves skeletal health [6, 18 , 21-23 , 26, 27].

Among available interventions, intravenous zoledronic acid has the strongest evidence for preserving BMD, while denosumab has demonstrated significant reduction in clinical fractures. The EBCTCG meta-analysis further suggests that adjuvant bisphosphonates may confer additional oncologic benefits in appropriately selected postmenopausal women [21]. The management algorithm emphasizes baseline fracture risk assessment, DXA evaluation, calcium and vitamin D supplementation, lifestyle modification, and timely initiation of antiresorptive therapy in patients at increased risk [20].

Overall, the available evidence supports a proactive, risk-adapted strategy for preserving bone health during adjuvant AI therapy. Early identification of patients at risk and prompt implementation of evidence-based preventive measures are essential components of comprehensive breast cancer survivorship care.

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Statement of Transparency and Principles

• The authors declare no conflict of interest.

• The study was approved by the Research Ethics Committee of the authors' affiliated institution.

• All authors contributed to the implementation of this research.

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