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Review

Osteoporosis in Postmenopausal Women with Breast Cancer

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Abstract

Breast cancer and osteoporosis are both diseases of aging. The "one in eight" lifetime risks of breast cancer occur primarily in the sixth, seventh, eighth, and ninth decades of life. One-third of postmenopausal women will experience an osteoporotic fracture. It is the coalescence of osteoporosis, breast cancer, and breast cancer treatments that, in some cases, increases the risks of osteoporotic fracture. That makes it imperative to assess risk factors, screen, and prevent or treat osteoporosis in postmenopausal women with breast cancer. Osteoporosis is primarily a genetic disease with a few modifiable risk factors. These risk factors include greater than two to three alcoholic drinks per day, current smoking, and decreased physical activity. The standard screening tool for osteoporosis is dual-energy x-ray absorptiometry (DXA) that gives a readout of T-scores of the lumbar spine, total hip, and femoral neck. The T-score is the number of standard deviations (SD) above or below the mean bone mineral density (BMD) of an average young adult of the same sex. For every SD below the mean BMD, the fracture risks double. Osteoporosis prevention and treatment do not differ in women with or without breast cancer. The difference is in breast cancer treatments, such as aromatase inhibitors (AI), which cause two to three-fold higher bone loss than average postmenopausal bone loss. Two classes of drugs for osteoporosis are oral and intravenous (iv) bisphosphonates and the receptor activator of nuclear factor kappa B ligand (RANKL) ligand inhibitor, subcutaneous (sc)

denosumab. All three prevent bone loss and reduce the likelihood of fragility fractures. The treatment choice depends upon patient and provider preferences, specific contraindications (e.g., renal insufficiency), compliance, and costs. Despite guidelines and algorithms for AI-induced bone loss, the screening and treatment of osteoporosis remain suboptimal in postmenopausal women with breast cancer.

Keywords
Osteoporosis; breast cancer; postmenopausal women

1. Introduction

The number of cancer survivors over age 65 years of age is increasing (Figure 1). By the year 2040, there will be 26 million cancer survivors in total. Osteoporosis is also a disease of aging and affects nearly 200 million individuals worldwide. One-third of postmenopausal women will experience an osteoporotic fracture. These fractures cause morbidity, mortality, economic impact and possibly are preventable.

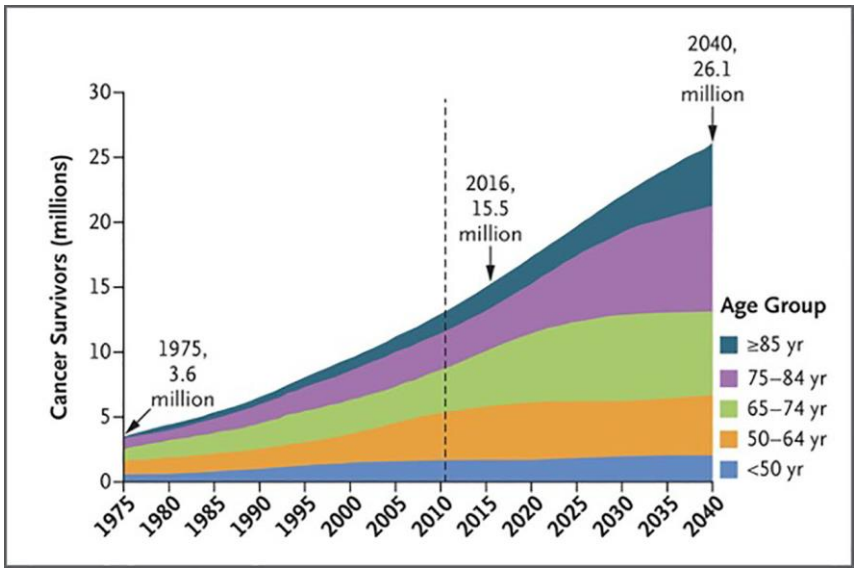


Figure 1 Cancer Survivorship over Time. The majority of cancer survivors now and in the future will be over the age the 65 years.

Bone loss and osteoporosis are commonly long-term (occurring during treatment and extending after treatment) and late-term (occurring after active treatment) adverse effects of breast cancer treatments [1, 2]. Postmenopausal women with breast cancer treated with aromatase inhibitors (AIs) are at greater risk of developing osteoporosis [2]. AI-induced bone loss occurs at a rate of two to three-fold higher than that of a healthy postmenopausal woman or one to two-fold-higher than postmenopausal women taking tamoxifen. As breast cancer survivors continue to live longer, the risk for developing osteoporosis and subsequent fractures also increases. Appropriate identification of the risk factors associated with osteoporosis, the diagnosis, and management of the disease is critical in mitigating bone loss and fractures and improving overall health outcomes.

2. Bone Remodelling and Osteoporosis

Bone is a dynamic tissue in a constant state of remodelling. Remodelling occurs in discrete areas of bone called remodelling units. Within the remodelling unit, there are three types of cells, osteoclasts, osteoblasts, and osteocytes. These three cells are responsible for bone resorption and new bone formation, respectively (Figure 2). The osteocyte is the master regulator of the bone remodelling unit. The osteocytes release RANKL and other osteoclastic cytokines *(i.e.*, interleukin (IL)-1, IL-6, IL-7, IL-8, and IL-11) responsible for osteoclast differentiation and bone resorption [3]. Osteoprotegerin (OPG), also secreted by osteocyte, serves as a decoy receptor for RANKL and, in effect, decreases osteoclast activation and promoting new bone formation. Also, the osteocyte secretes sclerostin. Sclerostin suppresses Wnt signalling, which is critical for bone formation. The ratio between RANKL and OPG governs bone resorption and new bone formation in normal remodelling and bone loss to normal aging, menopause, and AIs. (For a more extensive discussion of the osteocyte, see reviews by Creecy [4] and Kitaura [5]).

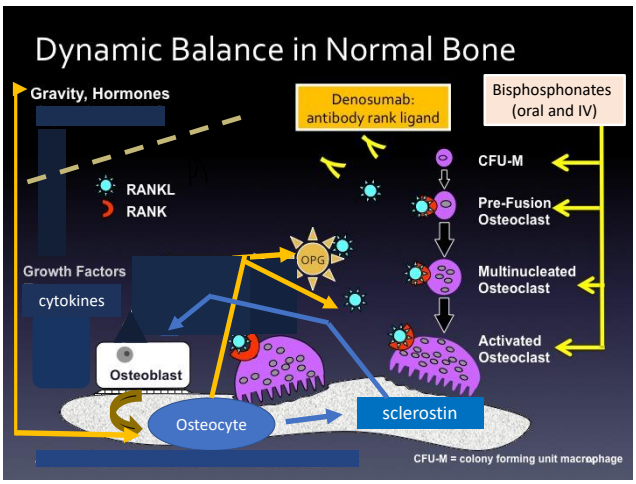


Figure 2 The Dynamic Balance of Bone Resorption and New Bone Formation. Two levels of regulation govern bone resorption and new bone formation. The Marco level is the effects of gravity, the mechanical stress and stains of activities of daily living, and systemic hormones including calcium-regulating hormones (parathyroid, calcitonin, and calcitriol), sex steroid hormones (estrogen and testosterone), and others (growth and insulin-like growth factor, thyroid hormones, and cortisol). At the Micro level is the dynamic interplay of osteoblasts, which cause new bone formation, osteoclasts that resorb bone, and osteocytes. The osteocytes are the master regulator cells secreting both receptor activator of nuclear factor-κB ligand (RANKL) and osteoprotegerin (OPG) of the TNF receptor superfamily [6]. RANKL binds to the Rank receptor and causes osteoclast precursor cells (derived from hematopoietic cells) to differentiate into mature osteoclasts and resorb bone. OPG acts as a decoy receptor for RANKL and causes inhibition of bone resorption and new bone formation. Also, osteocytes secrete sclerostin that inhibits osteoblastic new bone formation and stimulating bone resorption by secreting RANKL. Zoledronic acid (ZA) is an osteoclast inhibitor. In contrast, denosumab (DEN) is a monoclonal antibody directed against RANKL. Both drugs inhibit osteoclastic functions from resorbing bone and for preventing or treating osteoporosis.

The remodelling process of bone involves four overlapping stages. The first stage is the initiation of bone remodelling at a specific site. The second involves bone resorption by osteoclasts and the recruitment of mesenchymal stem cells that are the origins of osteoblasts. The third involves activation of osteoclasts, and the fourth is the mineralization of osteoid and completion of bone remodelling [7]. Normal bone remodelling is under tight control. However, the net loss of bone occurs in postmenopausal women due to aging and menopause. In addition to the interactions between osteoclasts, osteoblasts, osteocytes, gravity, mechanical stress, and strains of daily living activities, and several systemic hormones regulate bone remodelling. These hormones include estrogens (*i.e.*, estradiol, estrone), androgens (*i.e.*, testosterone), calcium-regulating hormones, including parathyroid, calcitonin and calcitriol, insulin-growth, thyroid hormones, and cortisol.

Estrogens are essential components in producing longitudinal bone growth, bone mass, and bone remodelling [8]. Estrogen inhibits bone resorption via direct action on osteoclasts [9]. Estradiol decreases by 85% to 90% in postmenopausal women relative to premenopausal women [10]. Decreasing circulating estrogen results in an acceleration of bone resorption and disrupts the tightly controlled balance in bone remodelling. Also, decreasing estrogen causes decreased intestinal calcium absorption and increased urinary calcium loss, contributing to bone loss [11].

Reduced bone mass caused by osteoporosis leads to micro-architectural changes in bone that result in fractures. One can think of osteoporosis as an equation. One part of the equation is peak bone mass, achieved by age 30, minus bone loss associated with aging and menopause [12]. Each equation is unique to the individual, based primarily on genetic factors. Genetic factors contribute to up to 75% of peak bone mass [13-15]. Studies demonstrate two hundred to more than five hundred loci associated with bone mineral density (BMD) and fractures [16, 17]. There are also single nucleotide polymorphisms (SNPs) associated with AI-induced bone loss or fractures [18, 19].

3. Risk Factors

There are several risk factors for developing osteoporosis [20]. Table 1 identifies the most significant risk factors. The most notable non-modifiable risk factor is a parent who has osteoporosis or suffered a non-traumatic fracture. Women with a maternal history of hip fractures are approximately twice as likely to experience hip fractures as women without a family history [21]. Also, it is essential to identify modifiable risk factors to promote bone health and overall health. A decrease in excessive alcohol consumption, smoking cessation, and increased physical activity can lower the overall fracture risk and promote overall health [22]. Secondary causes of osteoporosis further increase bone loss, including aromatase inhibitors (Table 1).

Table 1 Risk Factors for Osteoporosis.

Modifiable Risk Factors	Non-modifiable Risk factors	Secondary causes of osteoporosis
Alcohol consumption (>2-3 drinks/day)	Parental history of non-traumatic fracture	Chronic use of certain medications (steroids)
Cigarette smoking	Personal non-traumatic fracture*	Hyperparathyroidism

Inadequate nutritional status	Low body mass	Hypogonadism
Decreased physical activity	Gender	Rheumatoid Arthritis
	Age (> 50 years)	Diabetes, liver disease, chronic kidney disease,
	Ethnicity	Aromatase inhibitors

*Below age 50 years

4. Screening for Osteoporosis

Screening for osteoporosis does not differ in women with and without breast cancer. The most commonly used screening test for osteoporosis is the dual-energy x-ray absorptiometry (DXA) of the lumbar spine, hip, and femoral neck. The DXA provides bone mineral density (BMD) measurements. DXA scans report T and Z scores. The T score is the number of standard deviations (SD) above or below the mean BMD of an average young adult of the same sex between twenty and twenty-nine years of age. According to the World Health Organization, a T score of -1.0 and above is normal bone density. A T-score between -1.0 and -2.5 indicates osteopenia, and a T-score of -2.5 or below or having a fragility fracture is osteoporosis. The fracture risk increases nearly two-fold for every SD below the mean BMD for a young adult [23, 24]. Figure 3A illustrates the relationship between decreasing T-scores, increasing age, and hip fracture risks.

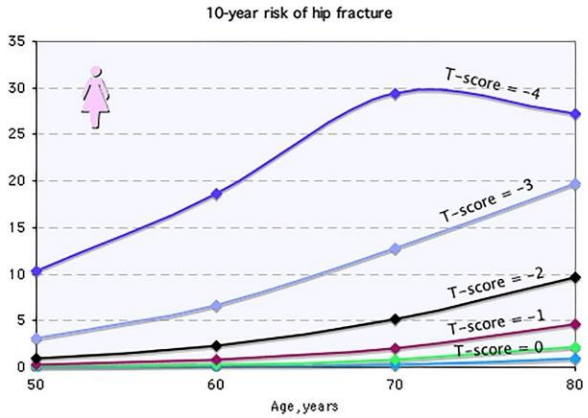


Figure 3 The 10-year Hip Fracture Risk by T-score and Age in the General Population. The fracture risk increases by age and T-score. For example, a 70-year-old with a T-score of -3.0 has a hip fracture risk of about 13% over the next 5-years.

A similar relationship exists between decreasing T-scores, increasing age, and the vertebral fracture risks (data not shown). Considering that many vertebral fractures are asymptomatic It is important to perform a dorsal and lumbar spine x-ray in order to see morphometric vertebral fractures. Indications for lumbar plain x-ray if the woman experiences a loss of height greater than 3 cm. An osteoporosis diagnosis should be established if vertebral or non-vertebral fragility has been identified irrespective of the T score. The Z score compares an individual's bone density with that of

an average person of the same age and sex and helps evaluate osteoporosis's secondary causes. If the Z-score is less than normal a secondary cause of osteoporosis is more likely. Osteoporosis has many secondary causes [25] (see Table 1 for a partial list of most common causes of secondary osteoporosis).

The DXA remains the gold standard for screening for osteoporosis. However, the DXA scan has its limitations. It provides a two-dimensional projection of a three-dimensional structure and does not capture the three-dimensional bone geometry or microarchitecture. Therefore, it does not represent an actual volumetric bone mineral density [26]. Frost outlines seventeen problems on the use DXA scans in his paper “Absorptiometry and “osteoporosis” problems [27]. Additionally, there is a lack of standardization in bone and soft tissue measurements, with discrepancies in measurements obtained on instruments from different DXA manufacturers. It is important to use the same DXA instrument for serial DXA screenings to accurately depict bone density changes over time.

5. Estimating the Fracture Risk

In addition to DXA scans, there are additional tools used to assess fracture risk. The Fracture Risk Assessment Tool (FRAX®) provides an assessment of fractures' prediction in men and women. FRAX® uses specific clinical risk factors with or without femoral neck bone mineral density [28]. These risk factors include age, sex, race, height, weight, body mass index, personal history of an osteoporotic fracture, parental history of hip fracture, use of oral glucocorticoids, rheumatoid arthritis, other secondary causes of osteoporosis, current smoking, and alcohol intake of three or more units daily. The algorithm calculates the ten-year risks of developing a hip or major osteoporotic fracture. Ten-year risk of a hip fracture that exceeds 3% or a 20% risk for overall major osteoporotic fractures warrants treatment with anti-resorption medications [29]. A DXA scan should be obtained at the initiation of the medication and then repeated at regular intervals.

Modifications to FRAX® when assessing AI-induced bone loss include checking “secondary osteoporosis” [30]. This practice is called into question by a Canadian-based registry cohort study. In the registry study, the designation of "secondary osteoporosis" as a risk factor for AI-induced bone loss overestimates fracture risks [31]. In multivariate analysis, women with breast cancer-initiating AI-therapy had a higher body mass index, higher BMD, lower osteoporosis prevalence, and fewer prior fractures than women not starting AIs or the healthy population [32]. The implications being AIs do not cause as many fractures as previously thought. These two studies are case-control registry studies and, as such, subject to several biases [33].

6. Calcium and Vitamin D

Calcium and vitamin D supplementation mitigate bone loss. However, calcium and vitamin D’s role in reducing fractures remains controversial. Both calcium and vitamin D plays a significant role in maintaining bone health. Along with phosphorus, calcium is part of the mineral component of bone. While it is stored primarily in bone and teeth, plasma calcium concentrations dictate calcium balance in the body. As plasma calcium decreases, bone resorption increases, impacting the architecture of bone [34, 35]. Vitamin D enhances intestinal absorption of calcium, maintaining serum calcium levels. Decreased concentrations of vitamin D disrupts plasma calcium homeostasis that can result in excessive bone resorption. Also, parathyroid hormone (PTH) plays a role in

maintaining calcium homeostasis. In the bone, PTH inhibits osteoblast activity and stimulates osteoclast activity leading to bone breakdown and calcium release. In the kidneys, PTH increases calcium reabsorption and blocks phosphate reabsorption from the tubules. Also, PTH acts at the kidneys to stimulate the formation of vitamin D [36, 37].

Ingested calcium is absorbed from the intestine passively and by mediated vitamin D active transport. Both mechanisms' efficiency decline with age and supplementation becomes necessary in maintaining bone health [38]. While the recommended dosage of calcium and vitamin D3 supplementation vary, most clinical guidelines recommend 1000-1200 mg of calcium (including dietary and supplemental) and 800-1000 IU of Vitamin D3 per day for women over the age of 50 [39]. Recommendations for postmenopausal women on AIs are similar, but studies remain limited in this area [40]. Vitamin D3 insufficiency (less than 30 ng/ml) or deficiency (less than 20 ng/ml) is common in the general population [41], and women with breast cancer [42], especially in minority populations [42]. Assess vitamin D3 levels either before starting AIs or when the baseline DXA shows osteopenia or osteoporosis.

A recent systematic review examined the evidence that calcium supplementation reduces the risk of fractures. The conclusions were that dietary calcium intake is not associated with a reduced risk of fractures [43]. Another systematic review and meta-analysis included 33 randomized clinical trials and over 51,100 individuals. The use of supplements that included calcium, vitamin D, or both was not associated with a significant difference in hip fracture risk than placebo or no treatment control in community-dwelling older adults [44].

7. Aromatase inhibitor-induced Bone Loss

Hormone receptor-positive breast cancers represent nearly seventy-five percent of all breast cancers. The AIs anastrozole, exemestane, and letrozole are the preferred treatment for postmenopausal women with hormone receptor-positive breast cancer [45]. The majority of postmenopausal women will be treated with an AI for five or ten years to reduce breast cancer recurrence risk and improve overall survival [46]. AIs work by inhibiting the P450 cytochrome CYP-19 or aromatase, responsible for converting androgens to estrogens [47, 48]. Aromatase is in tissues throughout the body, including breast, bone, brain, and ovary. AIs specifically inhibit aromatase that converts androgens to estrogens [49]. As AIs serve to reduce estrogen levels, this accelerates bone loss that will lead to osteoporosis and fractures in some women [2, 40].

Table 2 describes the risks of fractures with AIs or tamoxifen in the major trials in postmenopausal women [45, 50-53]. The AI-related fracture risk remains elevated during the treatment period of five years. During years five to ten, fracture rates decrease to those of tamoxifen. AIs also cause an increase in bone turn over markers which correlates loss of BMD, osteoporosis, and fractures [54]. However, the bone turnover markers are not, as yet, used for clinical decision making.

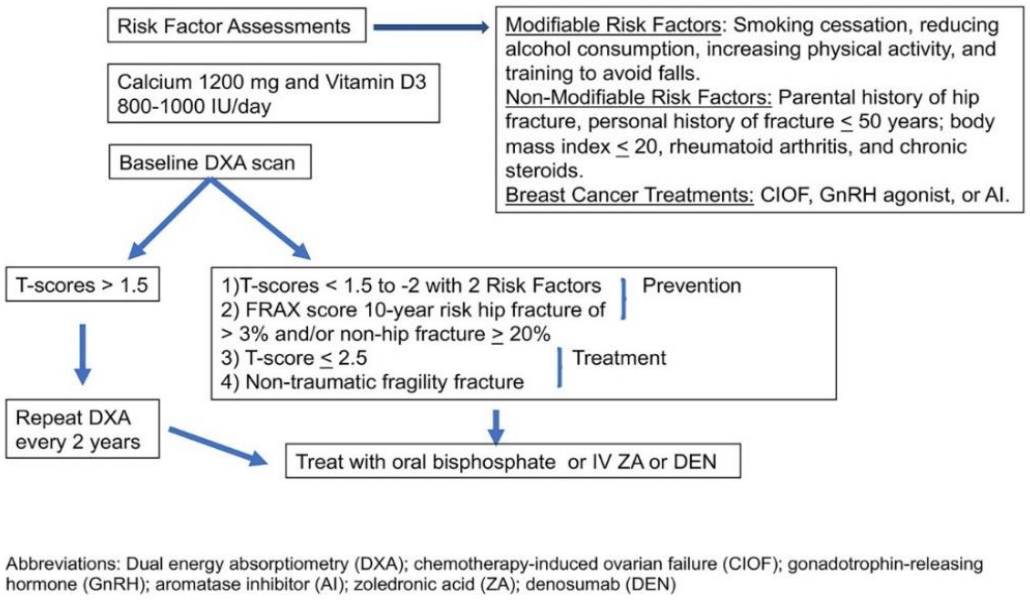
Table 2 Fractures Rates in Randomized Trials of Aromatase Inhibitors versus Tamoxifen.

Trial.	N	Follow-up (mo.)	Treatment	Fractures (%)	*p*-value	Ref
AI vs. Tam						
ATAC	9336	100	ANA vs. TAM	11 vs. 7.7	<0.001	[45]

BIG 1-98	4922	60	LET vs. TAM	9.3 vs. 6.5	0.002	[50]
AI after 2-3 yrs. of TAM						
TEAM	9779	61	EXE vs. TAM	5.0 vs. 3.0	0.0001	[51]
ABCSG8/ARNO	3224	28	ANA vs. TAM	2.0 vs. 1.0	0.015	[52]
AI after 5 yrs. of TAM						
MA-17	5187	63	LET vs. TAM	5.2 vs. 3.1	0.02	[53]

Abbreviations: Anastrozole (ANA); Exemestane (EXE); Letrozole (LET); Tamoxifen (TAM).

Figure 4 suggests an approach to AI-induced bone loss (modified from references [40] and [30]). It starts with risk factor assessment, addressing modifiable risk factors (i.e., reducing alcohol consumption, smoking cessation, encouraging physical activity and weight-bearing exercise), and consuming about 1200 mg of calcium (between dietary sources and supplements) and 800-1000 IU per day of vitamin D3. Obtain a baseline DXA scan and repeat regular intervals (e.g., every two years) and, depending on T-scores, institute anti-resorption drugs to prevent or treat osteoporosis (Figure 4).



Abbreviations: Dual energy absorptiometry (DXA); chemotherapy-induced ovarian failure (CIOF); gonadotrophin-releasing hormone (GnRH); aromatase inhibitor (AI); zoledronic acid (ZA); denosumab (DEN)

Figure 4 Algorithm for Bone Heath in Women with Breast Cancer. Assessment of fracture risk starts with dividing the risk factor assessment into modifiable and non-modifiable risks. Every woman should take 800-1000 IU/day of vitamin D3 and Calcium 1200 mg/day (made up of dietary sources and supplemental calcium). Vitamin D3 deficiency (20 ng/ml or less) or insufficiency (30 ng/ml) is common in the general population and breast cancer survivors and should be corrected. Obtain a DXA scan; if T-score is -1.5 or greater in the femoral neck, repeat DXA every two years. Institute treatment with an oral bisphosphonate, ZA or DEN if the T-score is less than -1.5 with two or more risk factors (i.e., receiving treatment with an AI, age over 65 years, family history of hip fracture, body mass index of less than 20, fragility fracture at age less than 50 years, or current smoking). If the FRAX® score shows that, major osteoporotic fracture risk is 20% or more, or the hip fracture risk is 3% or more institute drug therapy. (Algorithm modified from references [40] and [30]).

8. Drug Treatments for Osteoporosis

The drugs for osteoporosis treatment include oral and intravenous (iv) bisphosphonates and the RANKL inhibitor denosumab (DEN). Table 3 describes ZA and DEN [55-58]. The differences between ZA and DEN are their mechanisms of action, pharmacokinetics, administration, and costs. Table 4 describes the major trials of AI-induced bone loss [59-64]. Most of these trials rely on bone mineral density (BMD) as a surrogate for fractures. The one exception of the Austrian Breast Cancer Study Group (ABCSG) trial 18 [62]. ABCSG trial 18 was a double-blind placebo-controlled trial of DEN in over 3400 postmenopausal women receiving AIs. With six years of median follow-up, there was a 50% reduction in fractures (hazard rate (HR)=0.50 (95% CI 0.39-0.65). In the randomized controlled AZURE trial with a median follow-up of 7 years, there were 6.2% fractures in the iv ZA group and 8.3% fractures in the control group (hazard ratio (HR) 0.69 95% CI 0.53 to 0.90, p=0.005) [65].

Table 3 Comparison of ZA and Den.

Factor	ZA (iv)	DEN (sc)
Dose	4[@] or 5 mg[†]	60[@] or 120 mg[@μ]
Mechanism	Osteoclast inhibitor	RANKL monoclonal antibody
Metabolism	Not Metabolized	Not Metabolized
Half-life	2.5 hrs.,[*]188 days[¥]	28 days
Clearance	Renal	RES
Schedule	Every 6 months	Every 6 months
Common side effects	Fever, chills; muscle, bone or joint pain; nausea; fatigue; headaches	Joint, muscle pains; hypocalcaemia
Rare side effects	Osteonecrosis[¶]; renal insufficiency[§]; atypical femur fractures [66][¶]	Osteonecrosis[¶]; rebound vertebral fractures [67], and atypical femur fractures [68][¶]
Dose modifications	For creatine clearance < 60 ml/min modify ZA as follows: 50-60 min/ml = 3.5 mg 40-49 min/ml = 3.3 mg 30-39 min/ml = 3.0 mg Do not give ZA when the creatinine clearance < 30 ml/min	None
Costs[&] (US dollars)	252.00	1906.00

Abbreviations: zoledronic acid (ZA); intravenous (iv); denosumab (DEN); subcutaneous (sc); reticuloendothelial system (RES)

[@]Once every 6 months

[†]One dose annually approved non-cancer-related osteoporosis

[μ]The dose for skeletal metastases

[*]The half-life in the blood; [¥]Most goes to bone

[§]Dose-dependent and rate of infusion dependent

[¶]The incidence atypical femur fractures and osteonecrosis is well less than one percent.

[&]Costs of drug and administration from the Centers for Medicare and Medicaid Services Reimbursement (www.cms.gov)

Table 4 Major Trials of Anti-Resorptive Drugs in Aromatase inhibitor-induced Bone Loss.

Trial	Treatments	*n*	Results (L/S BMD)†	*p*-value	Ref
Brufsky	ZA 4 mg iv q6 mo for 1 yr vs. delayed	502	2.0 vs. −2.5	<0.001	[59]
Coleman	ZA 4 mg iv q6 mo for 5 yrs vs. delayed	1065	4.3 vs. −5.4	<0.0001	[60]
Ellis	DEN 60 mg sc q6 mo for 2 years vs. placebo	262	6.0 vs. −1.6	<0.0001	[61]
Gnant	DEN 60 mg sc q6 mo for 5 years vs. placebo	3425	HR fractures = 0.50 95% CI 0.39–0.65	<0.0001	[62]
Van Poznak	Risedronate oral 35 mg/week for 2 years vs. placebo	111	2.2 vs. −1.85	<0.0001	[63]
Sestak	Risedronate oral 35 mg/week for 3 years vs. placebo	150	1.1 vs. −2.6	<0.0001	[64]

Abbreviations: Zoledronic acid (ZA); denosumab (DEN); hazard ratio (HR); †percentage change in the lumbar spine per year.

8.1 Oral and IV Bisphosphonates

Figure 5 illustrates the nitrogen-containing bisphosphonates. Bisphosphonates have a high affinity for bone mineral matrix because they bind to hydroxyapatite crystals. When osteoclasts resorb bone, bisphosphonate is released and impairs the osteoclast's ability to complete bone resorption [69, 70]. Oral and iv bisphosphonates have a nitrogen-containing R2 side chain, promoting osteoclast apoptosis by interfering with intracellular signalling of critical regulatory proteins [71, 72].

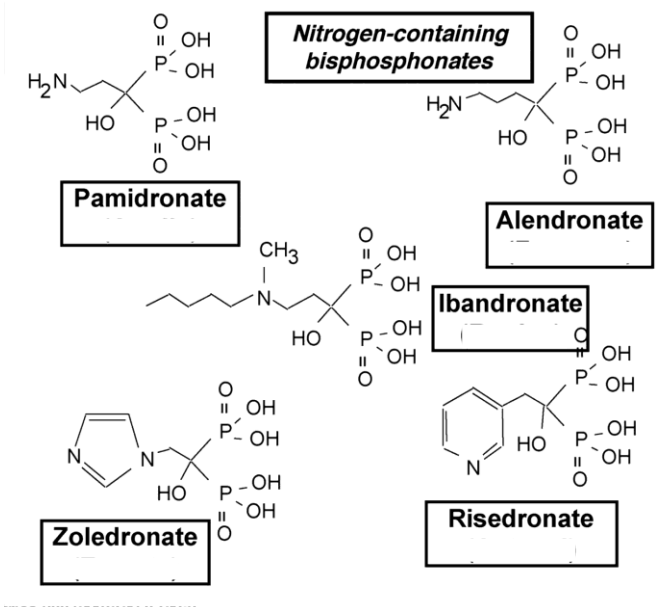


Figure 5 Structures of the N-amino Bisphosphonates. These drugs are analogs of inorganic pyrophosphate, a significant constituent of the bone mineral matrix. When osteoclasts take up the bone mineral matrix, the n-amino bisphosphonates inhibit farnesyl diphosphate synthase, responsible for converting dimethylallyl diphosphate to farnesyl diphosphate (FDP). Thus, leading to the inhibition of the post-translational modifications (or isoprenylation) of guanosine triphosphate (GTP)-binding proteins Rab, Rac, and Rho. These GTP binding proteins are critical for osteoclast resorption of bone.

Oral bisphosphonates, alendronate, risedronate, and ibandronate, are more commonly prescribed than iv bisphosphonates, but they are associated with low bioavailability, compliance considerations, and adverse drug reactions, including GI-related toxicities. ZA is the most potent iv bisphosphonate and can be given every six months or once yearly. ZA's side effects include an acute-phase reaction including myalgias and arthralgias, low-grade fever, and bone pain that often resolves within twenty-four to seventy-two hours post-infusion. Also, it causes renal insufficiency, and rarely atypical femur fractures and osteonecrosis of jaw [73].

Bisphosphonate dosing is calculated based on the estimated creatinine clearance rate (https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021223s028lbl.pdf). Avoid bisphosphonates in glomerular filtration rates of less than 30-35 mL/min [74, 75]. Both oral bisphosphonates, ZA, and DEN, are associated with the severe side effect of osteonecrosis of the jaw that is dose and duration-dependent. Dental screenings should occur before initiating therapy [76]. With osteoporosis treatment every six months, both DEN [77] and ZA [78] have a zero incidence of osteonecrosis. In non-clinical trial settings, the incidence may be slightly higher than zero. The risks of both drugs are rare, and the benefit-to-risk ratio favors treatment with anti-resorptive drugs.

8.2 Denosumab

DEN is a human form of a monoclonal to RANKL, thereby slowing bone resorption (Figure 2) [79, 80]. The FREEDOM trial (Fracture Reduction Evaluation of Denosumab in Osteoporosis every

Six Months) was a phase III, randomized, placebo-controlled clinical trial that compared denosumab 60 mg subcutaneously (SC) every six months and placebo in 7868 postmenopausal women with osteoporosis [81]. The primary efficacy endpoint was new vertebral fractures at 36 months. The denosumab group had statistically significant relative risk reductions for vertebral fractures (HR=0.32 95% CI 0.26-0.41, p,0.001), hip fractures (HR=0.40 95% CI 0.37-0.97, p=0.04), and non-vertebral fractures (HR=0.80 95% CI 0.67-0.95, p=0.01) compared with placebo. DEN is typically well-tolerated, administered every six months. The side effect profile includes the risk of rebound vertebral fractures after stopping DEN [82], asymptomatic hypocalcaemia, atypical femur fractures [68], and osteonecrosis of the jaw, similar to that of bisphosphonates [83]. In fact, the incidence atypical femur fractures and osteonecrosis of the jaw is well less than one precent with denosumab, zoledronic acid, and oral bisphosphonates.

9. Drug Choice

When deciding to prescribe anti-resorptive drugs, a comparative efficacy analysis shows that oral and iv bisphosphonates and DEN reduce fractures [84]. One is not superior to the other [84-86]. Limited head-to-head studies are comparing the effectiveness of ZA versus DEN in treating osteoporosis. In a large population-based cohort study, the risk of osteoporotic fracture was similar between ZA and DEN (HR=1.21 95% CI, 0.84 to 1.73). The two drugs have comparable clinical safety and effectiveness after one year of initiation [87]. In women with a history of breast cancer, the selection between oral bisphosphonates, ZA, or DEN depends upon patient and provider preference, specific toxicities (i.e., baseline renal toxicities), compliance considerations, and costs.

The American Society for Bone and Mineral Research formulated guidelines on the optimal duration of bisphosphonate therapy for postmenopausal women with osteoporosis [88]. The guidelines stratify women as low risk versus high risk for fracture. They advise assessing the risk of fracture at five years on oral BPs and three years on IV BPs. Those who are considered high-risk should continue to take oral BPs for up to 10 years or IV therapy for up to six years. Fracture risk should be reassessed every two years during extended therapy.

Postmenopausal women on AI therapy are at an increased risk for fracture and should be monitored closely for fracture risk through treatment duration. The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases recommends ZA, or DEN, be administered every six months for the entire AI treatment period for all osteoporotic women [89]. However, the authors disagree with this recommendation preferring to use the algorithm outlined in Figure 4. In the ZO-Fast trial results [60], only twenty-seven percent of the “delayed group" (the randomized ZA group only when the T-score was less than -2.0, or a fragility fracture occurred) received ZA during the first five years of the trial. That means eighty-three percent of women were over treated with ZA during the first five years of follow-up on the ZO-fast.

10. Anti-Cancer Effects of Anti-Resorptive Drugs

Anti-cancer effects of bisphosphonates and denosumab were observed in preclinical models [90, 91]. Disseminated tumor cells (DTCs) reside in the bone marrow and contribute to other sites of metastases [92]. DTCs serve as a prognostic factor in early breast cancer [93], and ZA can reduce DTCs in the human bone marrow [94, 95]. These observations led to the hypothesis that anti-

osteoporotic drugs not only mitigate bone loss and reduce fractures but have anti-cancer effects as well. This hypothesis was tested in the clinic.

Several randomized trials [62, 78, 96, 97] and meta-analysis restricted to bisphosphonates [98] show statistically significant reductions in distant metastases, skeletal metastases, and cancer mortality but are only observed in postmenopausal women. The Early Breast Cancer Trialists' Collaborative Group included over 6000 premenopausal and over 11,000 postmenopausal women. Whereas there was no effect in premenopausal women, there was an absolute reduction in bone metastases (2.2% p=0.0002) and cancer mortality (3.3% p=0.002) in postmenopausal women. In 2017 the Joint Canadian Care Ontario and American Society of Clinical Oncology Practice Guideline put out a statement saying that "consider" ZA (4 mg iv) every six months for three to five years, or oral clodronate (1600 orally/day, not available in the US) for three years in high-risk postmenopausal women [99]. Additional trials in postmenopausal women are needed to confirm the results of the meta-analysis [100].

Fifty-three percent of consensus participants said "yes," but 37% of them said "no" to the use of adjuvant ZA with ovarian suppression and AI or tamoxifen at St. Gallen/Vienna Consensus Discussion [101]. However, when queried about the use of adjuvant ZA, only 43% of consensus participants said "yes." Finally, the European Society of Medical Oncology recommends adjuvant bisphosphonates for those who undergo ovarian suppression or are postmenopausal, especially if they are at a high risk of relapse [102]. Thus, there is still considerable uncertainty about the use of adjuvant ZA.

Two other trials of denosumab are published. The randomized, placebo-controlled D-CARE of adjuvant denosumab vs. placebo [103], and Austrian Breast Cancer Study Group (ABCSG) trial 18 was another randomized placebo-controlled trial whose primary endpoint was fractures [62]. In D-CARE (n=4509), the denosumab schedule was intensive with sc every three to four weeks for the first six months, then every three months for five years. The D-CARE trial was wholly negative, even postmenopausal women. That is there were no reductions cancer mortality and bone metastases for the denosumab versus placebo-treated women.

ABCSG (n=3425) with six years of median follow-up, the disease-free survival (DFS) was statistically significantly higher in favor of the denosumab treatment (hazard ratio (HR)=0.82 95% CI 0.69 to 0.98, p=0.026) [77]. However, when one looks at hard endpoints (e.g., invasive local-regional and distant recurrences, invasive contralateral breast cancers, and deaths), there were no differences between denosumab and placebo. Contributing to “statistical significance” was non-histologically verified distant metastases and second breast cancers and non-breast invasive cancers.

Southwest Oncology Group (SWOG) trial of zoledronic acid vs. oral clodronate or ibandronate [104]. In the SWOG trial (n-6097), ZA's schedule was intensive with monthly iv for six months and every three months for three years, and doses of clodronate and ibandronate were 1600 and 50 mg/day, respectively. SWOG was a negative trial even divided by age (less or equal or greater than 55 years of age. Only about 40% of medical oncologists routinely use bisphosphonates in their “high risk” postmenopausal women [101], reflecting the literature's uncertainty and limitations.

A newer drug approved by the Food and Drug Administration for postmenopausal osteoporosis treatment is the monoclonal antibody romosozumab [105, 106]. Romosozumab binds sclerostin, produced by osteocytes, and increases new bone formation, and reduces fractures. A randomized, double-blind phase III comparing monthly sc romosozumab and weekly oral alendronate in over four thousand osteoporotic women showed a 48% reduction in vertebral fractures (HR=0.52 95% CI

0.61-0.66, p<0.001) with acceptable side-effects [105]. Romosozumab requires testing in breast cancer survivors for osteoporosis and in the metastatic setting. Also, newer RANKL inhibitors are in development [107].

11. Conclusions

Osteoporosis remains a growing concern worldwide, with approximately nine million osteoporotic-related fractures occurring every year [108]. It continues to be a prominent public health concern, particularly in the elderly. Postmenopausal women with a history of breast cancer on AIs are at an increased risk of developing osteoporosis and subsequent fragility fractures. Some of these fractures are preventable. Despite assessment tools and treatment guidelines, compliance with guidelines is not optimal [109]. The algorithm outlined in Figure 4 is a suggested approach for AI-induced bone loss. The choice between oral, IV bisphosphonates, or DEN, as all these drugs increase BMD and reduce fractures, depends on patient and provider, specific toxicities (e.g., renal toxicity), compliance, and cost considerations. Women with breast cancer should identify the provider (e.g., the primary care provider or specialty physician) depending on local expertise and practice patterns responsible for bone health.

Author Contributions

J Lamond participated in literature review, was responsible for the first draft, made comments on multiple drafts, and reviewed the final manuscript. CL Shapiro conceptualized the review, formulated the outline for the literature review, edited the first draft, responded to comments of the reviewers for the first and subsequent drafts, and reviewed the final manuscript.

Competing Interests

The authors declare no conflicts of interest.

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