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SCIENTIFIC REVIEW

Postmenopausal Breast Cancer, Aromatase Inhibitors, and Bone Health: What the Surgeon Should Know

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Abstract Breast cancer, as the most common malignancy in women, remains a major public health issue despite countless advances across decades. Endocrine therapy is the cornerstone of treatment of the hormone-sensitive subtype of breast cancer. The use of aromatase inhibitors (AIs) in the postmenopausal women has extended the survival beyond that of Tamoxifen, but harbors a subset of side effects, most notably accelerated bone loss. This, however, does not occur in all women undergoing treatment. It is vital to identify susceptible patients early, to limit such events, employ early treatment thereof, or alter drug therapy. International trials on AIs, predominantly performed in North American and European females, provide little information on what to expect in women in developing countries. Here, surgeons often prescribe and manage endocrine therapy. The prescribing surgeon should be aware of the adverse effect of the endocrine therapy and be able to attend to side effects. This review highlights clinical and biochemical factors associated with decrease in bone mineral density in an, as yet, unidentified subgroup of postmenopausal women. In the era of personalized medical care, appropriate management of bone health by surgeons based on these factors becomes increasingly important.

Abbreviations

AIs	Aromatase inhibitors
ATAC	Arimidex, Tamoxifen, alone or in combination
AEs	Adverse effects
BMD	Bone mineral density
BMI	Body mass index
BS-ALP	Bone-specific alkaline phosphatase
BIG 1-98	Breast International Group 1-98
CYP 19	Cytochrome P450 enzyme
CR	Clinical response
CTX	C terminal telopeptide
DNA	Deoxyribonucleic acid
DXA	Dual-energy X-ray absorptiometry
ER	Estrogen receptor
FRAX	Fracture Risk Assessment Tools
HER 2	Human epidermal growth factor 2
IOF	International Osteoporosis Foundation
IES	Intergroup Exemestane Study
LVA	Lateral vertebral assessment
NCIC CTG	National Cancer Institute of Canada Clinical Trials Group
NTX	Cross-linked *N*-telopeptides of bone type I collagen
NOF	National Osteoporosis Foundation

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NHANES	National Health and Nutrition Examination Survey
PTH	Parathyroid hormone
PR	Progesterone receptor
RANKL	Receptor activator of NF-κB ligand
SNPs	Single nucleotide polymorphisms
SDs	Standard deviations
25(OH) vitamin D	25 hydroxy vitamin D
WHO	World Health Organisation

Introduction

Breast cancer is the most common female cancer, globally [1]. In developing countries, it has replaced cervical cancer as the leading cause of cancer death in women [1]. These patients ideally, should be managed in multidisciplinary teams that coordinate surgical treatment in conjunction with the modalities of chemotherapy, irradiation, endocrine therapy, and biological therapy [2]. In developing countries, such as South Africa, this is often available only in major centers and mostly in tertiary hospitals affiliated with universities [3].

Determination of the molecular receptor status of tumors is standard in breast cancer classification. Routine testing for receptors in breast cancer includes the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER-2) [2]. Hormone-receptor sensitive breast cancer is the most common breast cancer subtype, and endocrine therapy is the cornerstone of systemic treatment [4].

Women with hormone receptor-positive disease have an excellent 5-year survival [5]. Endocrine therapy in the adjuvant setting for the postmenopausal status consists of treatment with Tamoxifen or Aromatase inhibitors [4]. Endocrine manipulation has systemic side effects. It is important to take cognizance of these and accurately quantify the potential for long-term morbidity [6].

In premenopause, ovaries are the principal source of estradiol. In post menopause, ovaries cease to produce estrogen, and circulating estrogen levels fall precipitously. Extragonadal sites such as adipose tissue, breast, bone, vascular epithelium, and brain produce estrogen locally from C19 steroid precursors via the aromatase Cytochrome P450 enzyme. Circulating estrogen levels therefore do not accurately reflect concentrations in local tissue, where estrogen acts in a paracrine or intracrine fashion [7]. In bone in particular, local estrogen production slows postmenopausal bone loss [7].

Bone health

Osteoporosis is characterized by compromised bone strength that predisposes to an increased risk of fracture [8]. Osteoporotic fractures occur in nearly 40 % of the postmenopausal woman. Menopausal women experience a sustained doubling of bone turnover [8] due to estrogen withdrawal and a subsequent increase in bone resorption. An accelerated loss of BMD of 1–3 % per year at the spine and 1–2 % per year at the hip has been observed in the first 7 years after the onset of the menopause.

This weakening of the bone structure decreases resistance to low-energy trauma and coupled with a low BMD increases bone fragility and fracture risk [9]. Major risk factors for osteoporosis comprise age, female gender, a personal history of fracture as an adult, a history of a fragility fracture in a first-degree relative, low body weight, current smoking and excessive alcohol consumption, and use of corticosteroids [10]. Other contributing factors are excess height, poor general health, and certain endocrine and systemic conditions. Poor depth perception and the use of drugs like benzodiazepines increase the risk of falling and so add to the fracture incidence.

The most common sites of fragility fractures are vertebrae, femoral neck, and distal radius [8].

Methods used to assess fracture risk include bone mineral density (BMD), biochemical bone markers, and the Fracture Risk Assessment Tools utilized in countries or regions with known hip prevalence figures.

Bone mineral density

Bone mineral density (BMD) is an assessment of the mineral content in key skeletal regions [11]. It is measured with dual X-ray absorptiometry and is expressed in absolute terms as grams of mineral per square centimeter scanned (g/cm^2). The T score is the number of standard deviations that a patient's bone mineral density value is above or below the reference value for a healthy 30-year-old adult.

Results are expressed as standard deviations (SDs) from age- and sex-matched standards (Z score) or from the population mean peak bone mass (T score). The reference range recommended by the International Osteoporosis Foundation (IOF), World health Organisation (WHO), and National Osteoporosis Foundation (NOF) for calculating the T score is the National Health and Nutrition Examination Survey (NHANES) III reference database for femoral neck measurements in Caucasian women aged 20–29 years [12]. Fracture risk increases roughly twofold for every standard deviation below the mean for a young adult. The WHO defines normal bone mass as $T > -1.0$, with osteopenia being $T < -1.0$ and $Z > -2.5$, and osteoporosis $T < -2.5$. Each SD represents a difference of 10–15 % in BMD. A T score of <-2, 5 is indicative of a 25 % loss from peak bone mass. Fracture risk increases exponentially with lower BMD. For T scores of -1.0,

−2.0, and −3.0, the relative risks of fracture are 1.7-, 3.4-, and 6.8-fold, respectively [8].

DXA-measured BMD is accurate and reproducible. It uses X-rays to assess BMD by area (not volume). The radiation dose is approximately one-tenth of a standard chest X-ray. Patients should have repeat BMD measured by the same machine and by the same operator, to minimize error [8]. It is the only bone density test that is currently useful for assessment of BMD changes over a time period and for determining the response to therapy [13].

Fracture Risk Assessment Tools (FRAX)

BMD provides the cornerstone for the diagnosis of osteoporosis, but it cannot be used in isolation as a determinant for the initiation of therapy [12]. The WHO's Fracture Risk Assessment Tool (FRAX) is a risk prediction model that employs the femoral neck BMD as measured by DXA and includes clinical factors for bone loss. It estimates the 10-year probability of hip and other major osteoporotic fractures (spine, humerus, and forearm). Clinical factors include country or geographic region, the patient's ethnic origin, age, sex, weight, height, prior fragility fracture, parental history of hip fracture, current smoking, excess alcohol intake, long-term use of oral glucocorticoids, rheumatoid arthritis, and secondary osteoporosis [11].

FRAX can be calculated for four ethnicities (white, Hispanic, Asian, and black) in a gender- and geographic-specific manner [8]. It allows entry of ages 40–90 years; there is no validation of FRAX in younger or older patients. FRAX cannot be used to monitor therapy as it considers only femoral neck bone density in the calculation of risk and allows only yes/no input rather than gradations of secondary risk factors. In the United States, the National Osteoporosis Foundation recommends treatment of patients with a FRAX-calculated 10-year fracture probability of >3 % for hip fracture and >20 % for major osteoporotic fracture [11].

A similar web-based tool, the FORE 10-Year Fracture Risk Calculator (http://riskcalculator.fore.org), closely aligns with the US regional data from the WHO-FRAX model offering similar risk estimates for men and women older than 45 years. FORE also allows entry of glucocorticoid dosing; allows information on spine fracture; and adds a graphic display showing low, moderate, or high 10-year fracture risk for use in patient education [8].

Biomarkers of bone turnover

The common use of aromatase inhibitors led to in an increased focus on cancer treatment-induced bone loss. Bone strength is a function of BMD and bone quality. Bone quality describes the set of characteristics that influence bone strength independently of BMD and include structural and material properties. Bone turnover is a function of the bone renewal process in which old or damaged bone is resorbed (bone resorption) and new bone is created (bone formation). Normally, bone resorption and formation is tightly balanced to ensure that bone mass and quality is maintained. Excess resorption and sustained increases in bone turnover not only result in decreased BMD, but may also adversely affect bone architecture and quality. These qualitative changes may decrease bone strength independent of BMD.

Biomarkers are used to assess the rate of bone turnover and can thus provide information on bone quality. Combining BMD and bone markers allows for the identification of a subcategory of individuals at an increased risk of hip fracture compared to those identified by each test in isolation [14].

The role of estrogen in bone health

Estrogen plays an integral part in bone metabolism in women and is fundamental in the pathogenesis of osteoporosis in postmenopausal women. The bone loss associated with estrogen deficiency is a complex and multidimensional process [15]. Estrogen is a systemic inhibitor of bone resorption by complex measures on bone cellular level [16]. The reduction of serum oestradiol at the onset of the menopause leads to a negative balance at the bone remodeling unit level [17]. The mechanisms by which estrogen regulates bone remodeling are not fully understood but estrogen is thought to affect osteoclastogenesis and osteoclast functioning through its effects on local cytokines and growth factors.

Endocrine therapy

There are two distinct subtypes of estrogen receptors, namely ER-α and ER-β. Tamoxifen has been used in the treatment of endocrine sensitive breast cancer for decades and it is the benchmark against which newer drugs are measured. Tamoxifen acts as a pure antagonist on ER-α in breast tissue, resulting in a decrease in breast cancer cell proliferation [18]. Conversely, it acts as an agonist on the estrogen receptor β expressed in bone and brain thereby promoting estrogen effects in these organs. This selective agonist effect of Tamoxifen in bone thus protects women against accelerated postmenopausal bone loss attributable to cessation of ovarian estrogen production [19].

An overall 19 % reduction in the incidence of fractures was seen in postmenopausal women receiving Tamoxifen

Table 1 Impact of endocrine therapy on BMD in postmenopausal women with breast cancer

Trials	Intervention	BMD changes (%)	*p* value	Fracture rate (%)
ATAC [6]	Arimidex	Hip: −7.24 Spine: −6.08	<0.01	11
	Tamoxifen, alone or in combination	Hip: 0.74 Spine: 2.77		7.7
NCIC CTG MA.17/ BIG 1–97 [6]	Letrozole (post Tamoxifen)	Hip: −3.4 Spine: – 4.1	0.009	5.3
	Placebo	Hip: *2* Spine: 1.0		4.6
IES [6, 24]	Exemestane post Tamoxifen	Hip: −2.9 Spine: −3.9	<0.001	7
	Tamoxifen (continued)	Hip: −1 Spine −0.6		4.9
Gonelli [6]	Tamoxifen	Hip: −2.01 Spine: −3.0	<0.01	Not available
	Exemestane (post Tamoxifen)	Hip: 0 Spine: 0.0		
BIG 1-98 [6, 17]	Letrozole (L)	Not available	0.002	5.7
	Tamoxifen (T)			4.0

therapy for a median of 5.75 years [20]. Tamoxifen use in the switch trials as well as extended duration of treatment beyond 5 years is well documented [18, 19].

Aromatase inhibitors heralded a new strategy in the treatment of breast cancer. These agents are without the estrogenic effects and have an improved side effect profile compared to Tamoxifen [21]. Today, it constitutes the gold standard in the treatment of endocrine responsive breast cancers in postmenopausal women.

The use of aromatase inhibitors (AIs) in postmenopausal patients is well-established. Several trials have documented a significant reduction of in-breast recurrence and contralateral breast cancer, as well as a reduction in the risk of distant metastases [22, 23]. The third-generation aromatase inhibitors demonstrate greater efficacy and superior overall safety in the adjuvant treatment of women with hormone receptor-positive breast cancer, compared with the selective estrogen receptor modulator Tamoxifen [24, 25].

The near total suppression of estrogen production by aromatase inhibitors has focused research on the aggravation of symptoms of menopause such as hot flashes and cardiovascular disease and have also raised significant concern regarding potential worsening of bone loss and the incidence of fragility fractures [26].

Bone loss and fracture

Aromatase inhibitors are the drugs of choice in postmenopausal breast cancer patients with endocrine responsive tumors. However, aromatase inhibitors enhance bone turnover and result in the loss of bone mass [27]. The general population risk factors for osteoporosis apply to breast cancer patients. However, cancer treatment causes additional bone loss that could increase the risk, above that seen in cancer-free women.

The level of bone loss and fracture risk is directly related to the further suppression of already low postmenopausal estrogen levels. In postmenopausal women, AIs decrease the serum levels of estrogen, beyond physiological levels and it is expected that bone loss would be augmented [28, 29]. The ATAC (Arimidex, Tamoxifen, alone or in combination) bone sub-protocol confirmed that adjuvant Anastrozole therapy can lead to accelerated bone loss in postmenopausal women with early breast cancer [30], compared to the bone -protective effect seen with Tamoxifen. This confers a two- to threefold higher risk of fractures versus women receiving Tamoxifen. Annual rates of bone loss from AI treatment range from 3 to 4 % at the spine and 1 to 2 % at the hip [31]. Hip fractures, associated with greater morbidity than all other osteoporotic fractures combined, did not differ between treatment groups, even with follow-up extending beyond the 5-year treatment period. The relative increase in fractures in the Anastrozole group remained constant over the 5-year treatment period but was not evident in year 6 [32, 33].

Most of the large clinical trials have evaluated bone loss rates of AI therapy and reported significant bone loss at lumbar spine and hip. (Table 1) The rates of bone density change after 1 year of AI treatment ranged from −1.66 to −7.40 %, a wide variation depending on the baseline characteristics of the patients studied [34].

Many trials lack data on baseline risk factors for fracture, including, older age, prior fracture, and other comorbidities, as well as the longer-term effect on bones. The objective of treatment is not only to ensure cancer-free survival, but to limit detrimental effects of therapy [6].

Bone turnover

Measurement of bone turnover markers can be used to examine changes in bone turnover in the short term [35]. ATAC and MA17 [19, 36], indicated statistically significant increases in both bone formation markers (e.g., osteocalcin) and bone resorption markers (e.g., cross-linked *N*-telopeptides of bone type I collagen [NTXs]) over the first 3–24 months of treatment of AI therapy. Studies examining AI-induced bone marker changes suggest a disparity between resorption and formation, leading to a net bone loss and increased fracture risk. Bone turnover marker profiles may be clinically useful in identifying those at highest fracture risk who require early intervention with anti-resorptive agents or, potentially a change in treatment [35]. The bone turnover changes occur early on in the initiation of AI treatment and, in the ATAC, MA-17, and IES trials [20, 36], bone loss has translated into increased fracture rates with AI use compared to Tamoxifen use [25, 35].

Body weight

The relationship between body weight, breast cancer risk, and breast cancer treatment is complex [37]. Estrogen has long been suspected as the hormone responsible for increasing breast cancer risk in obese postmenopausal women [38]. Aromatase resides in adipose tissue (among other tissues), leading to higher estrogen levels in heavier postmenopausal breast cancer patients. This higher level of estrogen may thus worsen breast cancer outcome, but may be bone-protective in this subgroup of postmenopausal women [39].

The adjuvant use of adjuvant AIs have increased the concern about long-term bone health and fracture risk [40]. Considering the bone-protecting effect of estrogen [41] and the hypothesis that concentrations of estrogen differ among lean and obese women, it is important to investigate bone health in accordance with BMI [39]. Endocrine therapies for breast cancer are not given by weight- or body-surface-area-related dosing; currently, one standard dosage applies to all patients [42].

On the other side of the spectrum, low body mass index (BMI) has long been associated with an increased risk of fracture [43]. The fracture risk associated with low BMI (<20 kg/m^2) is the strongest for hip fracture and is independent of age, gender, and BMD [43].

In the postmenopausal breast cancer patient population, there is marked variation in BMI. The increased fracture risk in the lean patient and the potential protective effect of estrogen in obese patients may thus influence the outcome of BMD changes in patients on AIs.

Vitamin D

Vitamin D is essential for the maintenance of the human skeleton [44, 45]. Wide variability in vitamin D levels occur due to differences in geographic location, season, sun avoidance behaviors, sunscreen use, increasing age and skin pigmentation, obesity, and other lifestyle factors [46]. The normal 25(OH)D values remain vague [47, 48]. The International Osteoporosis Foundation recommends a desirable 25(OH)D serum level of 30 ng/mL or above [47].

Deficiency in Vitamin D can cause secondary hyperparathyroidism, high bone turnover, low bone mineral density, and mineralization defects. Insufficiency can be a significant risk factor for osteoporosis [44] and could contribute to an increased fracture risk [34].

Vitamin D deficiency is very common among the general population, especially the elderly, [28] with up to 88 % of postmenopausal breast cancer patients having levels <30 ng/mL [49]. Adequate dietary calcium and vitamin D intake is important for maintaining BMD, but supplementation alone is not sufficient to prevent the accelerated bone loss that occurs during AI therapy [43].Vitamin D repletion to a target threshold of >40 ng/ml can have a protective effect on bone loss among low-risk patients on AI treatment [34]. Vitamin D level is currently not measured prior to initiation of AI therapy in a standard fashion but is strongly recommended if resources allow [50].

Guidelines for initiation of bone therapy for surgeons prescribing aromatase inhibitors

The importance of maintenance of bone health during adjuvant breast cancer therapy has led to the formulation of multiple guidelines regarding the need for bone-specific protection in the setting of AI therapy. These guidelines are very similar in their assessment of risk and recommendations [30, 40, 51]. Bone-specific protection therapy with bisphosphonates as first-line option is indicated in all women with a baseline bone mineral density in the osteoporotic range (T score ≥ -2.5SD below norm) and should be continued for the duration of AI therapy.

Patients with baseline BMD in the osteopenic range, i.e., a BMD T score between -1 and -2.5 below norm, also

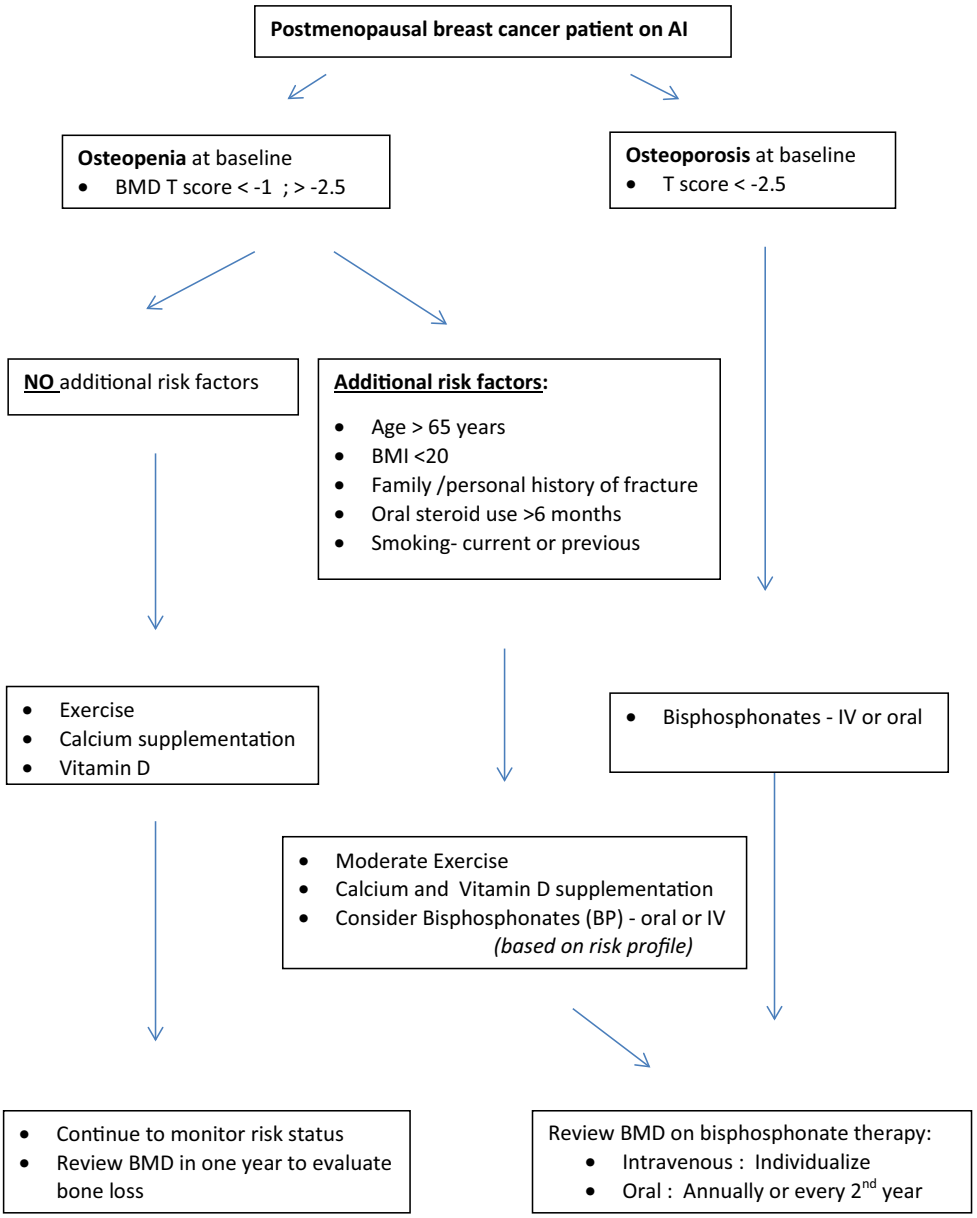

Fig. 1 Recommended algorithm for bone protection in postmenopausal breast cancer patients, on aromatase inhibitors (AI). Adopted with permission of Hadji et al. [41, 52]

qualify for bone-specific protection if additional risk factors for bone loss are identified at baseline or if they display accelerated bone loss during follow-up.

Recommended calcium supplementation in postmenopausal women is a total daily intake of 1200 mg (dietary AND supplementation). Supplementation per se should not exceed 600 mg daily. Recommended daily Vitamin D supplementation is 800–2000 IU.

Intravenous bisphosphonate therapy such as Zoledronic Acid is currently regarded the gold standard [52]. Oral bisphosphonates and Denosumab are other potential and very useful treatment options. Bisphosphonates suppress bone resorption. Side effects with oral bisphosphonates are mostly limited to reversible gastro-esophageal irritation. Severe suppression of bone turnover with osteonecrosis of the jaw (ONJ) or atypical fractures is a very unusual side effect and almost exclusively seen with the more potent intravenous preparations and longstanding use (beyond 5–10 years of therapy) [53, 54]. The advantage of preventing excessive bone loss and fractures with bisphosphonate therapy far outweighs the potential risk of these very unusual complications.

An adjusted protocol based on guidelines in the setting of adjuvant AI therapy for postmenopausal breast cancer patients is illustrated in Fig. 1 [51, 55].

Conclusion

The extended survival in breast cancer patients heightened the interest in the side-effect profile of therapies. The secondary aim of treatment should be to minimize morbidity for survivors and simultaneously maximizing the quality of life. In the era of personalized medicine, an early assessment of risk would facilitate individualized patient management decisions and provide an accurate estimate of disease outcomes and side effects. This would aid in measures to prevent or limit adverse events and to assist the clinician/surgeon in early drug modification to potentially avoid the side effect in this sub-group of susceptible women or to minimize harmful effects.

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Compliance with ethical standards

Conflict of interest None.

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