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Review

Prevalence of Bone Fractures in Women with Breast Cancer: A Systematic Review of the Impact of the Use of Aromatase Inhibitors

Adriele Godgienski [1], Emanuela Lando [2,#], Julia Pastorello [3], Rosana Martins [1]

[1] Atitus Educação, Passo Fundo, Rio Grande do Sul, Brazil.
[2] Hospital de Câncer de Barretos, Barretos, São Paulo, Brazil.
[3] Department of Medical Oncology, Hospital de Clínicas de Passo Fundo – HCPF, Passo Fundo, Rio Grande do Sul, Brazil.

* Correspondence: manu.lando@hotmail.com.

Abstract: The prevalence of bone fractures in patients with breast cancer undergoing treatment with aromatase inhibitors (AIs) is associated with a substantial increase in the risk of osteoporotic fractures and loss of bone mineral density (BMD), due to suppression of bone mineral levels, estrogen in the body, especially in postmenopausal patients. In essence, the present study aims to evaluate the prevalence and severity of bone fractures in breast cancer patients who are being treated with AIs, as well as identify the related risk factors. A systematic literary review was conducted using the scientific databases PubMed and Scielo, the keywords aromatase inhibitors, breast cancer, bone mineral density and fractures were used. Included were publications between June 2002 and February 2021. A total of 176 studies were identified (PubMed: n = 120; Scielo: n = 56), of which 126 were excluded for not meeting the eligibility criteria. Ultimately, 15 studies were included in the analysis, comprising 13 from PubMed and 2 from Scielo. The AIs has a significant impact on BMD in postmenopausal patients, especially compared to patients treated with tamoxifen, and is evident in studies that analyzed the transition from tamoxifen to AI. This negative effect on BMD is related to the increased risk of fractures in patients with hormone receptor-positive breast cancer, especially patients with BMD T-scores less than -1,5. It is relevant that different AIs have varying effects on bone health; anastrozole is associated with a more pronounced reduction in BMD than letrozole and exemestane. In addition to preserving bone health, the inclusion of biphosphonate agentes and vitamin D supplementation demonstrated efficiency in reducing the risk of BMD.

Keywords: Oncology; Breast cancer; Aromatase inhibitors; Bone mineral densit.

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1. Introduction

Breast cancer is one of the most diagnosed malignancies in women worldwide, requiring multifaceted therapeutic approaches to improve survival and quality of life of patients [1]. In the context of hormone therapy, aromatase inhibitors (such as anastrazole, exemestane and letrozole) play a crucial role. These agents prevent the conversion of androgens to estrogens, thereby reducing circulating levels of estrogen, which is essential for the growth of estrogen receptor-positive breast cancer cells [2, 3]. However, as more women are treated with aromatase inhibitors, concern is growing about the effects of these drugs on bone health [2-5]. Osteoporosis and fracture risk become significant con-

cerns, particularly as many patients are diagnosed at ages when bone health is already compromised [2-5].

In this systematic review, we examine the relationship between long-term aromatase inhibitor use and bone fracture prevalence in women with breast cancer. Through analysis of recent observational studies and clinical trials, we identify specific fracture patterns and associated risk factors. This understanding is crucial for developing improved management strategies and personalized treatment approaches, ultimately enhancing patient care and safety throughout treatment and survivorship.

2. Method

A comprehensive literature search was performed using PubMed and SciELO databases. Search terms included 'aromatase inhibitors,' 'breast cancer,' 'bone mineral density,' and 'fractures,' covering publications from February 2001 to June 2022. Predefined inclusion and exclusion criteria were established. We included Only clinical studies, controlled trials, and cohort studies examining aromatase inhibitors' effects on bone mineral density (BMD) and fracture risk in postmenopausal breast cancer patients. Case reports and unrelated studies were excluded.

A total of 176 studies were identified (PubMed: n = 120; Scielo: n = 56), of which 126 were excluded for not meeting the eligibility criteria. Ultimately, 15 studies were included in the analysis, comprising 13 from PubMed and 2 from Scielo.

3. Results

Reduced estradiol levels in women are correlated with decreased bone mineral density (BMD) and increased risk of fractures. Third-generation aromatase inhibitors (AIs), such as anastrozole, letrozole, and exemestane, are used to treat early and advanced breast cancer [2-5]. These agents significantly reduce estrogen levels in postmenopausal women [6]. However, due to their mechanisms of action, there is concern about the implications of these drugs on bone tissue, especially when used as adjuvant treatment [2,6-7]. The ATAC (Anastrozole and Tamoxifen Alone and in Combination) study, which included 9,366 postmenopausal women with breast cancer, evaluated the efficacy and safe-ty of anastrozole and tamoxifen alone or in combination. After a mean follow-up of 68 months, the results showed that anastrozole was associated with a higher incidence of fractures than tamoxifen (11% vs 7.7%, odds ratio = 1.49; 95% CI, 2.25 to 1.77) [8].

The ATAC study, which compared the effects of antiestrogen therapy with anastrozole and tamoxifen, included a subprotocol to assess the impact of the treatments on the bone health of patients. The results demonstrated that anastrozole increased bone remodeling activity and impaired BMD, while tamoxifen and the combination of the two drugs increased BMD [8-9]. Postmenopausal women with breast cancer were enrolled in a BMD study as part of adjuvant treatment. Patients with (T-score values > -2.5) indicative of osteoporosis were included in the archival study, while those with (T-score values between -1 and -2.5) indicative of osteopenia were included in the medical classifications. Women not treated after breast cancer surgery were included as a reference group. Additional exclusion criteria were applied to participants in the BMD study that did not apply to the main study [8-9].

The main analysis focused on the change in BMD of the lumbar spine and hip over time. Conclusions were made at baseline and repeated after 1, 2, and 5 years of experimental treatment. To assess the BMD of the lumbar spine, the mean values of the L1, L2, L3 and L4 vertebrae were used. As for the total BMD of the hip, this was calculated from the relationship between the global bone mineral content and the bone area in the trochanteric, intertrochanteric and femoral neck regions of the hip [8-9].

To detect a 2.5% difference in bone mineral density variation between the anastrozole and tamoxifen groups, with 90% statistical power and a 5% significance level, at least

67 patients were required in each group. Considering possible disease recurrences and resistance, it was recommended to recruit 86 patients in each treatment group [8-9]. A total of 308 postmenopausal women from nine countries participated in the bone sub-protocol after being randomly assigned to treatment in the ATAC trial. Of these, 197 received monotherapy and 108 (55%) were evidence-based after 5 years (57 with anastrozole and 51 with tamoxifen) [8-9]. In addition, 46 postmenopausal women with breast cancer who did not accept treatment after primary surgery were recruited as a control group, of which 30 were eligible for 5-year analysis.

At baseline, approximately 45% of women protected with anastrozole, 48% with tamoxifen, and 49% of the control group had no osteopenia in the lumbar spine, whereas 36% of each group had osteopenia without hip. The mean baseline bone mineral density at the lumbar spine was 1,071 g/cm² for the anastrozole group, 1,039 g/cm² for the tamoxfen group, and 1,055 g/cm² for the control group. The mean bone mineral density for the total hip was 0.942 g/cm² in the anastrozole group, 0.911 g/cm² in the tamoxifen group, and 0.927 g/cm² in the control group. It is important to note that more patients in the anastrozole group were within 1 year of menopause compared with the tamoxifen and control groups.

Overall, 59 patients (35.3%) who received monotherapy in the study failed to complete this sub study (24 [29.6%] on anastrozole and 35 [40.7%] on tamoxifen). Among these patients, eight on anastrozole and 14 on tamoxifen were discontinued during the 2-year analysis and were therefore archived from the 5-year analysis. The most common reasons for discontinuation over the 5 years were adverse events and investigator decisions. Notably, women who discontinued the study after 1 year (but not after 2 years) experienced more rapid bone density loss than those followed for 5 years with both anastrozole (p=.006) and tamoxifen (p=.05) at the lumbar spine (but not at the total hip) [8-9].

In the group of women treated with anastrozole, a specific increase in median bone mineral density (BMD) was observed in both the lumbar spine (-6.08%) and total hip (-7.24%) over the 5-year period. In contrast, the group receiving tamoxifen showed an in-crease in median BMD over the 5 years (lumbar spine, +2.77%; total hip, +0.74%). This increase was notable in the first 2 years, with no additional variation in years 2 to 5. The discrepancies between the treatment groups were statistically significant in both areas (p<0.0001). In contrast, the control group experienced changes in median BMD over the 5 years (lumbar spine, +1.35%; total hip, -2.97%). The results showed that the anastrozole group had a significant decrease in BMD at the lumbar spine and total hip, while the ta-moxifen group had a slight increase in BMD at the lumbar spine over the first 2 years. Pa-tients in the untreated control group had little change in BMD at the lumbar spine and a small decrease in BMD at the total hip. None of the patients who maintained a normal BMD at baseline developed osteoporosis at 5 years. However, more women receiving anastrozole became osteopenic compared with those treated with tamoxifen, and some patients with initial osteopenia developed osteoporosis during treatment. The study also found that the critical T-score for the development of osteoporosis was approximately -1.5 [8-9].

Statistical analysis revealed that treatment had a significant impact on changes in spine BMD (p<0.0001) and that the interaction between treatment and years since menopause affected spine BMD (p=0.03) but not hip BMD. This five-year study indicated a significant loss of BMD in the spine and hip over the five years with anastrozole compared with tamoxifen. However, there was a slowing of bone loss in the lumbar spine between the second and fifth years compared with the first year. The influence of anastrozole was most notable in the first four years after menopause. The control groups are not ideal comparators, and tamoxifen has a protective effect on bone due to its partial action on bone receptors. Third-generation aromatase inhibitors, including anastrozole, have been associated with an increased risk of fractures [8-9].

To Women with BMD T-scores below -1.5 are at increased risk of developing osteoporosis during treatment. This means that many patients are not allowed to undergo additional monitoring, except for those with pre-existing osteopenia or other risk factors. In these cases, regular BMD monitoring and bone protection strategies may be possible. Overall, the study suggests that anastrozole may lead to accelerated bone loss in women with postmenopausal breast cancer. However, this risk appears to be restricted to patients who already have osteopenia at baseline. Bone loss can be controlled by regular BMD testing and the use of bisphosphonates, making this aspect manageable and not an obstacle to the use of aromatase inhibitors in women with breast cancer [8-9].

In the MA.17 study extended by the National Cancer Institute of Canada Clinical Trials Group, women (N = 5,187) initially received tamoxifen for 5 years. They were then evaluated for an additional 5 years of treatment and divided into two groups, one group receiving letrozole (n = 2,593) and the other group receiving placebo (n = 2,594). During a 30-month follow-up period, patients receiving letrozole had a significantly increased incidence of newly diagnosed osteoporosis (8.1%) compared with the placebo group (6%) [10].

Two clinical trials evaluated the impact of aromatase inhibitors on bone mineral density (BMD) and fracture risk in postmenopausal women with breast cancer. The BIG 1-98 study showed that letrozole increased the risk of fracture by 42% compared with tamoxifen in 8,010 patients [11]. The Exemestane Intergroup study compared exemestane with tamoxifen in 4,724 patients who had already received tamoxifen for 2-3 years. Exemestane was associated with a 27% increased risk of fracture and a 4% loss in lumbar BMD at 24 months [11].

The BIG 1-98 clinical trial, a phase 3 study, was scheduled from March 1998 to May 2003. Its objective was to investigate the effects of letrozole compared with tamoxifen in the postoperative treatment of 8,010 postmenopausal women with hormone receptor positive invasive breast cancer. [11] Participants were randomized into four treatment groups, consisting of: tamoxifen monotherapy (20 mg daily) for 5 years, letrozole monotherapy (2.5 mg daily) for 5 years, sequential therapy with tamoxifen for 2 years followed by letrozole for 3 years, or sequential therapy with letrozole for 2 years followed by tamoxifen for 3 years. Allocation of participants into two-arm groups of letrozole or tamoxifen occurred from March 1998 to March 2000, while allocation into four-arm groups was per-formed between April 1999 and May 2003. In this specific analysis, we are focusing on results obtained from data from 4,895 patients who were randomized to the monotherapy groups (both two-arm and four-arm groups) in the context of the BIG 1-98 study and who received at least some study-related medication [11].

Regarding the incidence of bone fractures and multiple fractures, it was observed that, overall, the occurrence of bone fractures was more pronounced in patients who underwent treatment with letrozole [Letrozole: 228 of 2,448 women (9.3%), compared with those who received tamoxifen [Tamoxifen: 160 of 2,447 women (6.5%)]. The incidence of fractures, when stratified by grade, showed a similar trend between the treatment groups. Regarding multiple bone fractures during treatment, an increase in the occurrence was also distributed among patients who received letrozole [Letrozole: 23 of 2,448 women (0.9%)] compared with those who received tamoxifen [Tamoxifen: 10 of 2,447 women (0.4%)]. [11] Within the group receiving letrozole, fractures occurred most frequently at the following sites: wrist (recorded in 68 patients), femur (33 patients), thoracic spine (27 patients), humerus (25 patients), and ankle (21 patients). In contrast, in the tamoxifen-treated group, the most common sites for fractures were the wrist (observed in 34 patients), thoracic spine (22 patients), rib (22 patients), and ankle (14 patients) [11]. Treatment with letrozole demonstrated a higher incidence of bone fractures ($p=0.002$) compared with tamoxifen [11].

Compared with the results of the recent International Exemestane Study (IES) Report, which evaluated exemestane after two or three years of tamoxifen treatment before randomization, we found that the incidence of bone injuries in the present study, with

patients assigned to letrozole, was 27.08 per 1000 woman-years, higher than the 19.2 per 1000 woman-years reported in the exemestane group in the IES [12]. Another notable discrepancy between the IES and the BIG 1-98 is the occurrence of fractures of the hip, wrist, and spine, which were rare and not reported in the IES. The Cohort Study of Women on Long-Term AI Therapy was an observational study examining the risk of fractures in postmenopausal women with breast cancer on long-term treatment with breast aromatase inhibitors (AIs). The results suggest that, at baseline, women taking aromatase inhibitors had characteristics that compensated for the potential adverse effects of AI exposure, such as a higher body mass index and higher bone mineral density. Therefore, these patients did not show a significantly higher risk of fractures compared with the general population [11, 12].

Data from 6 large, rigorous studies show that aromatase inhibitors (AIs) with or without steroids cause bone loss and more fractures in breast cancer patients. For example, in the ATAC study, women taking anastrozole had nearly twice as many fractures as healthy, age-matched women with osteopenia (2.2% vs. 1.3% per year) [8,9]. Each study contributed to our understanding of the impact of AIs on bone health and fracture risk in postmenopausal breast cancer patients, emphasizing the importance of monitoring bone health during treatment with these agents [8-9].

Table 1. Effects of aromatase inhibitors associated with tamoxifen on bone health in patients with breast cancer who are positive for hormone receptors.

Drug Comparison	Year	Sample Size	Dose	Duration (years)	Outcome / Results	Reference
Anastrozole vs. Tamoxifen (ATAC)	2008	57 vs. 51	1 mg/day vs. 20 mg/day	5	BMD Lumbar spine: -6.8% vs. +2.7% Hip:-7.4%vs.+0.74%	[5]
Exemestane vs. Continue Tamoxifen	2007	4274 (randomized); 206 assessed	25 mg/day vs. 20 mg/day	5	BMD change: Year 2: -1% vs. -0.8% (hip) No difference in fracture rate in year 5: 7% vs. 5%	[13] [2]
Letrozole vs. Tamoxifen (GRANDE 1-98)	2009	2,448 vs. 2,477	2.5 mg/day vs. 20 mg/day	5	Percentage of fractures: 93% vs. 3.5%	[16]
Anastrozole vs. Exemestane	2014	153 vs. 147	1 mg/day vs. 25 mg/day	2	BMD: -2.39% vs. -0.92% Hip: -2.71% vs. -1.93% Fractures: 8% vs. 9.3%	[14]
Anastrozole vs. Letrozole	2017	2075 vs. 2061	1 mg/day vs. 2 mg/day	5	Osteoporosis: 10.9% vs. 10.9%	[18]
Anastrozole vs. Letrozole vs. Exemestane	2018	1175 vs. 1175 vs. 177	1 mg/day vs. 2.5 mg/day vs. 2.5 mg/day	5	Osteoporosis: 4% (Anastrozole) vs. 5% (Letrozole) vs. 5% (Exemestane)	[4]

4. Discussion

Breast cancer is a condition characterized by an uncontrolled dermatosis of breast cells [1]. In many cases, this is the norm driven by the presence of estrogen receptors (ER)

on tumor cells, the estrogen, a female hormone, normally stimulates cell growth in the mammary glands. However, in breast tumors expressing estrogen receptors (ER+), a hormonal stimulus results in cancer progression [2-4]. The role of aromatase inhibitors are drugs that act by inhibiting aromatase, an enzyme responsible for converting androgen into estrogen in the peripheral tissues of the body [2-5]. Reducing estrogen levels is beneficial in containing the growth of cancer cells in ER+ tumors however, this reduction in the female hormone has an impact on bone homeostasis [2-5]. Therefore, there is a decrease in bone mineral density, making bones more fragile and susceptible to fractures [15,16]. Estrogen plays a fundamental role in regulating the balance between bone formation by osteoclasts and bone resorption by osteoclasts [16].

Estrogen deficiency, resulting from the use of aromatase inhibitors, disturbs this balance, leading to decreased bone mineral density and bone fragility. Estrogen deprivation that occurs with natural menopause or associated with cancer treatment increases bone turnover and osteoclast activity, causing bone resorption and formation to become unbalanced, compromising microarchitecture and degree of mineralization [12-18]. Bone quality is increasingly recognized as an important determinant of overall bone health, and studies have shown that substantial deterioration of bone microarchitecture can occur before bone density is affected [12-16].

There are different generations of aromatase inhibitors, which are essential drugs in the treatment of breast cancer [2-5]. The first generation includes substances such as immunoglutethimide, ofedrazol and fornestan, third generation inhibitors, such as anastrozole, letrozole and exemestane, are currently considered the most relevant. Aromatase inhibitors are divided into two categories: inhibitors and inactivators. Inhibitors are steroids, such as anastrozole and letrozole, which act temporarily, acting as competitors for the aromatase enzyme [2-5].

On the other hand, inactivators, such as exemestane, bind permanently to the enzyme, deactivating it permanently, all of these drugs are called aromatase inhibitors and play a crucial role in blocking aromatase, which is associated with the production of estrogen, so controlling estrogen levels is essential in the treatment of breast cancer, especially in cases where the tumor is fueled by this hormone [1-4]. Different types of inhibitors offer doctors a variety of options to customize treatment according to individual needs [1-4]. The results of these studies clearly indicate that the use of aromatase, such as anastrozole, letrozole and exemestan, has a significant impact on bone mineral density in postmenopausal women [9-14]. There was a reduction notable increase in BMD in patients undergoing these treatments, compared with those who received tamoxifen therapy. This negative effect on BMD is an important concern as it is directly related to increased risk of fractures in patients with hormone receptor-positive breast cancer [9-16]. It is interesting to note that different AIs can have varying effects on bone health. For example, anastrozole appears to be associated with a greater reduction in marked increase in BMD than letrozole or exemestane [6-11]. This suggests that the choice AI may play a crucial role in managing the risk of bone loss in breast cancer patients.

In addition to the decrease in BMD, the risk of fractures is a significant concern, data indicate that patients treated with AIs have a substantially greater number of fractures compared to those that continue with tamoxifen. This is particularly evident in studies that analyzed the transition from tamoxifen to AI [16]. Understanding this risk is essential for clinical decision making and appropriate counseling for patients. The results of these studies raise questions about the need for mitigation strategies to preserve bone health in patients with breast cancer breast undergoing treatment with AIs. This may include consideration of agent's additional therapeutics, such as bisphosphonates, which have been shown to be effective in reducing the risk of fractures in patients undergoing treatment with AIs.

Furthermore, the importance of regular monitoring of BMD during treatment with AIs is emphasized to allow for early interventions. It is crucial to consider that not all patients present the same risk of bone loss and fractures. In addition to the type of AI

used, individual factors, such as body mass index and initial bone mineral density, affect a role in susceptibility to bone loss. Therefore, the clinical approach must be personalized, taking these characteristics into account.

4. Conclusion

Aromatase inhibitors (Ais), including anastrozole, letrozole, and exemestane, have been found to be effective in reducing breast cancer recurrence in postmenopausal patients. However, they are also associated with a significant loss of BMD and a significantly higher risk of fractures compared with tamoxifen, a selective estrogen receptor modulator. This negative effect on BMD is related to the increased risk of fractures in patients with hormone receptor-positive breast cancer, especially patients with BMD T-scores less than -1,5. It is relevant that different AIs have varying effects on bone health; anastrozole is associated with a more pronounced reduction in BMD than letrozole and exemestane. In addition to preserving bone health, the inclusion of biphosphonate agentes and vitamin D supplementation demonstrated efficiency in reducing the risk of BMD. Furthermore, the importance of regular monitoring of BMD during treatment with AIs is emphasized to allow for early interventions.

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