

Research Paper

Assessment of Aromatase Inhibitor-Induced Bone Loss and Appropriateness of Supportive Therapy in Postmenopausal Breast Cancer Patients at a Tertiary Care Center

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Abstract

Objective: To assess aromatase inhibitor-induced bone loss (AIBL) and its management in postmenopausal women (PMW) with breast cancer (BC). **Materials and Methods:** A cohort of 350 PMW with BC receiving aromatase inhibitors (AIs) during a span of 4 years was evaluated retrospectively. Bone mineral density (BMD) of the patients at lumbar spine (LS) and dual femur was monitored at baseline and annually for 2 years. Baseline fracture risk was evaluated using WHO fracture risk assessment tool. **Results:** At baseline, only 35.4% of the patients received supportive therapy such as calcium and Vitamin D supplements $\pm$ bisphosphonates. Significant decrease of mean BMD occurred at LS, left femur, and right femur (LF and RF) at 1 year ($P < 0.001$) in 64.6% of patients who did not receive supportive therapy at baseline. Those who received supportive therapy at baseline had a significant elevation of their mean BMD at LS, LF, and RF; ($P < 0.001$) at 1 year, and this increase in BMD persisted at 2 years. Ten-year fracture risk at baseline was 'high' for 3.14% of patients, while 35.43% had 'moderate risk' of major osteoporotic fracture and 26.6% had 'high risk' of hip fracture. Overall incidence of fractures was 1.1% in patients who did not receive supportive therapy from baseline to 1 year. **Conclusion:** Majority of BC patients on AIs were not prescribed supportive therapy at baseline. Since AI monotherapy caused significant loss of LS and dual femur BMD at 1 year of treatment, up-front supportive therapy should be started concurrently with AIs from baseline for the prevention of AIBL.

Keywords: Aromatase inhibitors, bisphosphonates, bone mineral density, breast cancer, calcium, Vitamin D supplements

INTRODUCTION

Breast malignancy is the most widely diagnosed neoplasm in women worldwide, with an estimated 2.1 million new cases in 2018, leading to a significant morbidity.^[1,2] Incidence of breast malignancy in India is less than that of western countries with an approximate annual incidence of 144,000.^[3] At our study center, 1600 new cases of breast neoplasm were diagnosed during the last 5 years. Majority of these patients were in the age group of 50–59 years, and 66.8% of the patients were treated with hormonal therapy.^[4] Around 60% of breast malignancies express estrogen receptors, suggesting the need of estrogens for tumor growth and progression.^[5] Currently, aromatase inhibitors (AIs) are the gold standard for the treatment of hormone-dependent breast malignancy in postmenopausal women (PMW). AIs block the transformation of androgens to estrogens in peripheral tissues via aromatization and

thus decrease estrogen-dependent tumor growth.^[6,7] Since estrogen is a principal regulator of bone formation, AI can be associated with elevated bone turnover, leading to bone loss, osteopenia, and osteoporosis, thereby increasing the risk of fractures. Hence, reduction in bone mineral density (BMD) is an inevitable consequence of such a treatment.^[8] There has been a greater awareness of elevated bone loss and fracture risk with the use of AIs, with an increasing attempt for

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appropriate interventions to decrease bone loss and prevent fractures.^[9] However, there is a paucity of data from India regarding aromatase inhibitor-induced bone loss (AIBL) and its management. Hence, this study was undertaken to get an insight into the degree of bone loss induced by AIs and assess the appropriateness of prescribing supportive therapy in breast cancer (BC) patients receiving AIs at a tertiary care center.

MATERIALS AND METHODS

A retrospective observational study of PMW, who received AIs for the treatment of BC from January 2012 to December 2015, was conducted in the Department of Medical Oncology, Amrita Institute of Medical Sciences and Research Centre (a 1250-bedded tertiary care center) in Kochi, Kerala, India. The list of patients receiving AIs during the study period was obtained from digital Amrita Hospital Information System (AHIS). The study population consisted of 904 patients who received AIs during the study period. All the 350 patients who satisfied the inclusion and exclusion criteria were recruited for the study [Figure 1]. Data were collected through direct examination of the patient's medical records and through the digital AHIS. Ten-year risk of hip fracture and major osteoporotic fracture was determined by WHO Fracture Risk Assessment tool (FRAX)^[10] developed by the International Osteoporosis Foundation. BMD at lumbar spine (LS), left femur (LF), and right femur (RF) was monitored based on dual-energy X-ray absorptiometry (DEXA) scan findings

documented in the patient's medical records. All the patients were followed up annually for 2 years. The study protocol was approved by the Institutional Ethics Committee (Approval No. IEC-AIMS-2017-PHARM-362) before screening of patients for enrollment. Requirement of 'patient consent' was waived since it was a retrospective chart review without any direct interaction with the patients.

The primary outcome measures were the percentage change of mean BMD at LS and dual femur and incidence of osteoporosis and fractures from baseline to 1 year and from 1 to 2 years of patients receiving AI monotherapy and patients receiving AIs with supportive therapy. The secondary outcome measure was percentage change of mean BMD at LS and dual femur of patients who received AIs with calcium and Vitamin D and patients who received AIs with calcium and Vitamin D + bisphosphonates from baseline to 1 year and from 1 to 2 years.

Supportive therapy consisted of calcium and Vitamin D supplements $\pm$ bisphosphonates. The American Society of Clinical Oncology (ASCO) guidelines^[11] was used to assess the appropriateness of supportive therapy. BMD was measured by DEXA imaging (Lunar prodigy advance DEXA system manufactured by GE Healthcare). Osteoporosis and osteopenia were assessed by T-score based on BMD measurements at LS, LF, and RF at baseline and after 1 and 2 years of therapy. Difference between a patient's BMD and that of a healthy young adult was measured in units called standard deviations (SDs). T-score was calculated as difference between a patient's measured BMD and the mean BMD of the young gender-matched normal population, divided by the SD of the BMD of the young normal population.^[12] The T-score was used to categorize the patients based on the WHO criteria for PMW: a T-score of ≥ -1 SD was considered 'normal' and a T-score of -1 – -2.5 SD as 'osteopenia' while a T-score of ≤ -2.5 SD was considered 'osteoporosis'. Z-score was calculated by comparing a patient's BMD to that of an age-matched group. Z-score was defined as difference between a patient's measured BMD and the mean BMD of the age-matched group divided by the SD of the BMD of the age-matched group. Z-score was characterized as a number of SDs by which the BMD of an individual differs from the mean value expected for age. A Z-score ≤ -2 was considered below the expected range for age and a Z-score > -2 as within the expected range for age.^[8] T-score and Z-score values were generated by the DEXA machine.

Statistical analysis

Statistical analysis was conducted using IBM SPSS Statistics for Windows, Version 20.0. (Armonk, NY: IBM Corp.). To obtain the characteristics of categorical variables such as medications and outcome, frequency and percentages were applied, and for characteristics of numerical variables such as age and BMD, mean and SDs were used. Results were expressed as percentage change in mean BMD at LS and dual femur from baseline to 1 and 2 years of follow-up, with

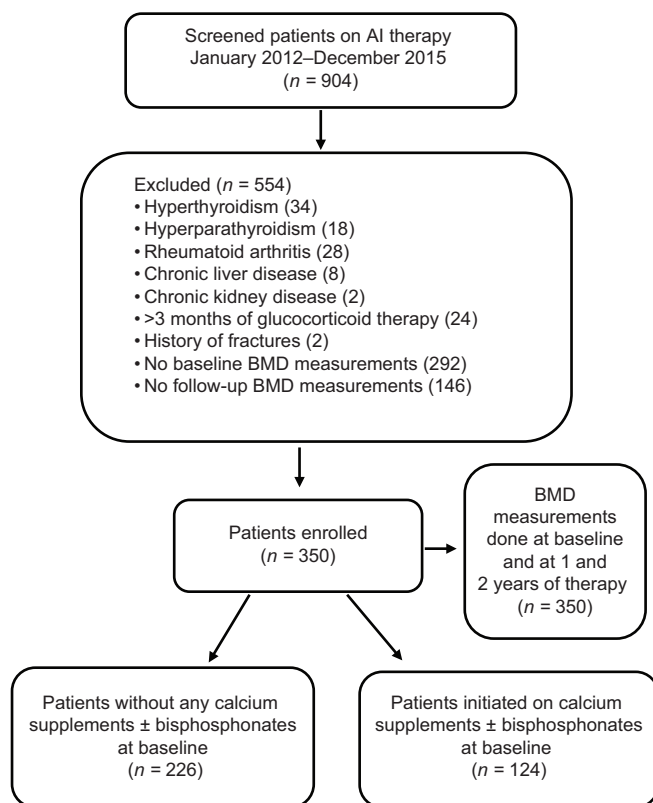


Figure 1: Schematic representation of patient selection process
AI = Aromatase inhibitors, BMD = Bone mineral density

corresponding 95% confidence intervals (CIs). Statistical significance was based on two-sided *P* values, and a 5% significance level was used. Pearson Chi-square test was employed for comparison of percentage change in mean BMD from baseline to 1 and 2 years of follow-up, and a *P* < 0.05 was considered statistically significant.

RESULTS

A total of 350 postmenopausal BC patients were evaluated for AIBL. The mean age of the patients was 65.14 ± 9.23 years (median 65 years, range 40–89 years, and CI: 64.17–66.11). Most of the patients had ductal carcinoma (87.5%, 306/350) followed by lobular carcinoma (9.4%, 33/350) and the remaining patients had both ductal and lobular carcinoma. Majority of the patients (55.1%, 193/350) had a tumor size of 10–19 mm followed by 36.9% (129/350) of patients with a tumor size of >20 mm and the remaining with a tumor size of 0–9 mm. High proportion of patients (57.1%, 200/350) had ‘moderate’ histological grade followed by 24.9% (87/350) of patients with ‘high’ grade and 18% (63/350) of patients with ‘low’ histological grade. A large number of patients (63.1%, 221/350) were strongly estrogen receptor positive (>80%), and the remaining patients were of moderate estrogen receptor positivity (50%–80%). Majority of the patients (64%, 224/350) had negative Human Epidermal Growth Factor Receptor (HER) 2 status and the remaining patients (36%, 126/350) were of positive HER 2 status. High proportion of patients (53.4%, 187/350) had positive nodes followed by 46.6% (163/350) of patients with negative nodes.

At baseline, majority of patients (61.43%, 215/350) had low fracture risk (<10%) followed by 35.43% (124/350) of patients with moderate fracture risk (10%–20%) and 3.14% (11/350) of patients with high risk (>20%) of major osteoporotic fracture (neck of femur, forearm, humerus, and spine). Risk of hip fracture was also low (<3%) in a high proportion of patients (73.4%, 257/350) followed by 26.6% of patients with high risk ($\geq 3\%$) of hip fracture. Patients with high risk of hip fracture were in the age group of 71–80 years, whereas a high proportion of patients with moderate and high risk of major osteoporotic fractures were in the age group of 61–70 and 71–80 years, respectively. Mean frequency of BMD assessment by DEXA was 12.01 ± 1.54 months (range 12–14 months).

Majority of the patients were prescribed letrozole (2.5 mg, once daily [OD], per oral [PO]) followed by exemestane (25 mg, OD, PO) and anastrozole (1 mg, OD, PO) [Figure 2]. At baseline, AIs were prescribed principally as monotherapy and the remaining patients who had either baseline osteopenia or osteoporosis were prescribed AIs in combination with calcium and Vitamin D supplements $\pm$ bisphosphonate [Table 1]. Calcium supplements (calcium carbonate 500 mg OD, Vitamin D₃ sachet 60,000 IU, weekly PO) and a combination of calcium supplements with bisphosphonates were the major supportive therapy. Injection zoledronic acid (4 mg, intravenous [IV] infusion, every 6 months) was the only bisphosphonate administered to the study patients. Those patients who had

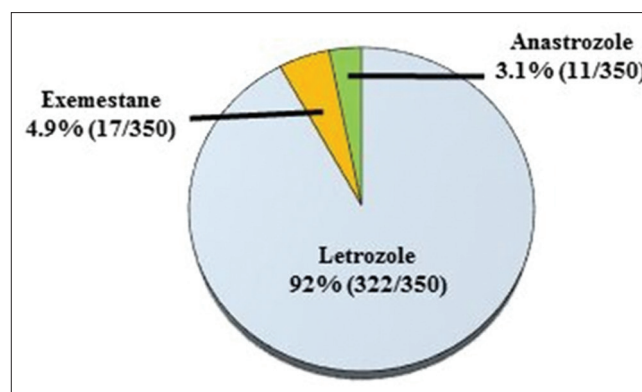


Figure 2: Prescribing pattern of aromatase inhibitors in the study patients (*n* = 350)

low fracture risk (61.4%, 215/350) were not prescribed any supportive therapy at baseline, and their BMD was reduced at 1 year of AI monotherapy. At 1 year from baseline, all the patients were prescribed supportive therapy along with AIs, but majority was prescribed only calcium supplements [Table 1].

There was a significant decrease of mean BMD at LS, LF, and RF at 1 year (*P* < 0.001) in patients who were not initiated on supportive therapy. After initiation of supportive therapy at 1 year of AI therapy, there was significant elevation in mean BMD of LS and dual femur at 2 years (*P* < 0.001). However, for patients who received supportive therapy right from baseline along with AIs, there was a significant elevation (*P* < 0.001) in mean BMD of LS and dual femur at 1 year as well as at 2 years [Figure 3 and Table 2].

Percentage elevation in mean BMD of the patients at LS, LF, and RF from 1 to 2 years as well as at RF from baseline to 1 year was also significant [Table 3]. Although there was increase in mean BMD at LS and LF from baseline to 1 year in patients receiving calcium and Vitamin D supplements + bisphosphonates when compared to those receiving calcium and Vitamin D supplements without bisphosphonates, the percentage change in mean BMD was nonsignificant (*P* = 0.148 at LS and *P* = 0.057 at LF). Effect of supportive therapy on T-score at LS and dual femur from baseline to 1 year followed by 1–2 years as well as from baseline to 2 years is shown in Tables 4 and 5, respectively.

Number of patients with Z-score ≤ -2 (below the expected range for age) at LS decreased from 5.7% (20/350) at baseline to 3.7% at 1 year (*P* < 0.001) and from 3.7% (13/350) to 0% at 2 years. Similarly, at dual femur, maximum patients (99.4%) were within the expected range for age and only 0.6% (2/350) of patients was below the expected range for age. After 1 year of AIs along with supportive therapy, only one patient was below the expected range for age and remaining patients were within the expected range for age. However, at 2 years, all the patients were within the expected range for age (*P* = 0.939).

Incidence of fractures in our study patients was 1.1% (4/350) all of whom were at moderate risk of fracture at baseline.

Only one patient (0.4%, 1/350) without supportive therapy at baseline experienced minimal trauma fracture at wrist and 0.8% (3/350) of patients experienced high trauma fracture at neck of femur, humerus, and spine, respectively, as confirmed by X-ray imaging. Patients initiated on supportive therapy along with AIs did not experience any fractures.

DISCUSSION

Our study confirms bone loss in PMW treated with AIs for BC. Majority of the patients were not prescribed either calcium and Vitamin D supplements or combination of calcium supplements and bisphosphonates at baseline. There was a significant elevation in BMD of LS and dual femur at 2 years in patients who received calcium supplements and bisphosphonates combination therapy at baseline as compared to those receiving calcium and Vitamin D supplements. Patients who received AIs without calcium supplements and antiresorptive therapy had a significant decrease in BMD at 1 year, but the BMD of all the patients increased from 1 year onward with the initiation of supportive therapy. For patients who received supportive therapy at baseline, there was a significant gain in BMD at 1 and 2 years.

Although AIs are prescribed in PMW, some of our BC patients prescribed AIs were in the age group 40–50 and 50–60 years, but these patients underwent oophorectomy before initiation of AIs because, in the premenopausal women, almost 95% of estrogen production takes place in the ovaries.^[5] Hence, AIs are not effective in the premenopausal women due to their inability to block ovarian production of estrogens.

Age >60 years is one of the important risk factors of BMD loss which in turn elevates the risk of fracture in PMW with breast malignancy.^[6,13] Our study patients had a mean age of 65.14 ± 9.23 years and 71.5% (250/350) of our patients were >60 years old. At baseline, 3.2% and 35.4%, respectively, of our patients had ‘high’ and ‘moderate’ risk of major osteoporotic fracture and 26.6% of patients had ‘high’ risk of hip fracture. PMW >60 years of age with breast neoplasm receiving AIs should therefore be advised about annual BMD monitoring, bone loss, and its prevention. At baseline, fracture risk assessment^[14] with FRAX and BMD are better than that with BMD alone^[10,15] for the identification of increased fracture risk and to make a decision about pharmacological interventions to improve bone health. Of 904 patients receiving AIs, only 38.7% (350/904) patients could be recruited for the

study mainly due to lack of BMD data on 48.5% (438/904) of patients. The reasons for this might be logistic, financial, or personal. Hence, patient education and physician awareness are necessary regarding annual measurement of BMD.

A trial done by Ingle *et al.*^[16] suggested that AIs are more efficacious to decrease the risk of disease recurrence in PMW with hormone-dependent breast malignancy compared to tamoxifen adjuvant therapy, but AIs can have a negative effect on bone mass.^[17-19] In our study also, BMD loss was observed in a high proportion (64.6%, 226/350) of patients for whom AI monotherapy was prescribed at baseline. Currently, third-generation AIs are mostly prescribed due to their greater efficacy. Among third-generation AIs, letrozole was preferred over exemestane and anastrozole in our study patients because letrozole reduces almost 99% of estrogen level which helps to inhibit tumor growth of breast malignancy^[5] and also because the cost of letrozole is much less compared to anastrozole and exemestane. At baseline, majority of our patients were prescribed letrozole without supportive therapy. Such supportive therapies were not initiated for a large number (226/350) of our patients may be because of the fact that their T-scores were normal (>–1 SD) at baseline. However, at 1 year of follow-up, all the patients were prescribed AIs in combination with supportive therapies due to decrease in

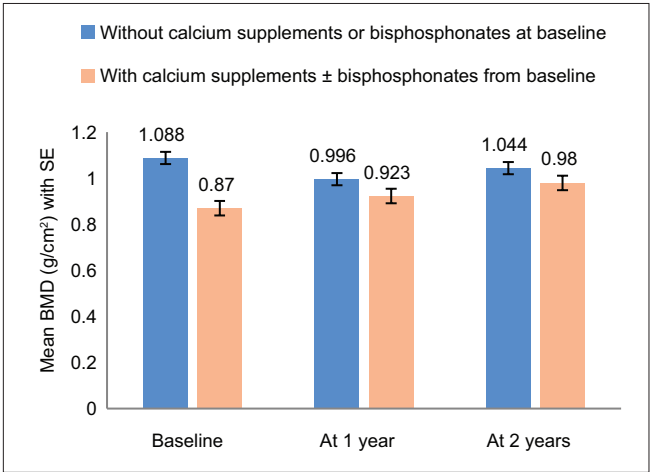


Figure 3: Change in mean bone mineral density of lumbar spine at 1 and 2 years of aromatase inhibitor therapy in patients with and without supportive therapy. At one year, all the patients received supportive therapy. The change in bone mineral density in both the groups was significant at 1 and 2 years of therapy (*P* < 0.001). SE = standard error

Table 1: Pattern of prescribing aromatase inhibitors as monotherapy and as combination therapy			
Therapy pattern	Number of patients (n=350)		
	At baseline, n (%)	At 1 year, n (%)	At 2 years, n (%)
AI monotherapy	226 (64.6)	0	0
AI combination therapy			
AI + calcium with Vitamin D	64 (18.3)	290 (82.9)	242 (69.1)
AI + calcium with Vitamin D + bisphosphonate	60 (17.1)	60 (17.1)	108 (30.9)

AI=Aromatase inhibitor

BMD at LS and dual femur. A great number of our patients were prescribed calcium and Vitamin D supplements along with AIs rather than bisphosphonates due to the high cost of bisphosphonates.

Our results directly establish that PMW receiving AIs without supportive therapy will have significant loss of BMD after 1 year at LS and dual femur and those who receive calcium

and Vitamin D supplements $\pm$ bisphosphonates from baseline will have a significant gain in BMD. The results of BMD loss [Table 2] observed in our study at LS, LF, and RF at 1 year (–8.5%, –8.3%, and –8.3%, respectively) was greater than the BMD loss observed by Kalder *et al.*,^[20] where exemestane caused significant reduction of mean BMD at LS and femoral neck at 1 year (–3.6% and –2.4%) and

Table 2: Effect of calcium and Vitamin D supplements $\pm$ bisphosphonates on percentage mean change of bone mineral density at dual femur at 1 and 2 years of aromatase inhibitor therapy

Site of BMD measurement	Interval of BMD monitoring	Mean change in BMD		P (Chi-square test)
		g/cm ²	Percentage (CI)	
LF	Without calcium supplements** or bisphosphonates at baseline (n=226)			
	Baseline to 1 year	−0.08	−8.3 (8.2-8.4)	<0.001
	1-2 years	0.05	5.6 (5.5-5.8)	<0.001
	With calcium supplements** or bisphosphonates at baseline (n=124)			
	Baseline to 1 year	0.043	5.2 (5.0-5.6)	<0.001
	1-2 years	0.045	5.2 (4.7-5.7)	<0.001
RF	Without calcium supplements** or bisphosphonates at baseline (n=226)			
	Baseline to 1 year	−0.08	−8.3 (8.1-8.4)	<0.001
	1-2 years	0.06	6.8 (6.7-6.9)	<0.001
	With calcium supplements** or bisphosphonates at baseline (n=124)			
	Baseline to 1 year	0.051	6.3 (5.8-6.8)	<0.001
	1-2 years	0.051	5.9 (5.6-6.4)	<0.001

**Calcium and Vitamin D supplements. BMD=Bone mineral density, CI=Confidence interval, LF=Left femur, RF=Right femur

Table 3: Comparison of percentage increase in mean BMD at lumbar spine and dual femur of patients who received treatment with calcium and vitamin D supplements or combination therapy of calcium and vitamin D supplements + bisphosphonates at baseline along with AIs

Site of BMD monitoring	Intervals of BMD monitoring	Percentage increase in mean BMD (CI)		P, (Chi-square test)
		Calcium and vitamin D supplements (n=64)	Calcium and vitamin D supplements + bisphosphonates (n=60)	
LS	Baseline to 1 year	5.2 (5.1-5.4)	7.3 (7.0-7.4)	0.148
	1 year to 2 years	3.4 (3.9-4.5)	7.9 (7.8-8.0)	0.002
LF	Baseline to 1 year	4.9 (4.2-5.6)	7.2 (6.6-7.8)	0.057
	1 year to 2 years	3.9 (3.7-4.3)	7.5 (6.5-8.4)	0.001
RF	Baseline to 1 year	5.6 (5.1-6.1)	7.8 (6.8-8.8)	0.038
	1 year to 2 years	4.9 (4.3-5.3)	7.9 (6.8-8.9)	0.003

AIs: Aromatase inhibitors; BMD: Bone mineral density; CI: Confidence interval; LS: Lumbar spine; LF: Left femur; RF: Right femur

Table 4: Categorization based on T-score at lumbar spine of patients without or with calcium and Vitamin D supplements $\pm$ bisphosphonates at baseline along with aromatase inhibitors

Site of BMD monitoring	Intervals of BMD monitoring	Percentage of patients			P (Chi-square test)
		Normal	Osteopenic	Osteoporotic	
LS	Without calcium supplements** ± bisphosphonates at baseline (n=226)				
	Baseline	82.3	17.3	0.4	
	At 1 year	14.2	74.8	11.0	<0.001
	At 2 years	34.0	63.8	2.2	<0.001
	With calcium supplements** ± bisphosphonates at baseline (n=124)				
	Baseline	2.4	41.1	56.5	
	At 1 year	6.5	58.0	35.5	<0.001
	At 2 years	19.4	71.8	8.8	<0.001

**Calcium and Vitamin D supplements. BMD=Bone mineral density, LS=Lumbar spine

Table 5: Categorization based on T-score at dual femur of patients without or with calcium and Vitamin D supplements ± bisphosphonate at baseline along with aromatase inhibitors

Site	Intervals of BMD monitoring	Percentage of patients			P (Chi-square test)
		Normal	Osteopenic	Osteoporotic	
LF	Without calcium supplement** ± bisphosphonate at baseline (n=226)				
	Baseline	99.6	0.4	0	
	At 1 year	44.7	54.5	0.8	<0.001
	At 2 years	83.6	16.4	0	<0.001
	With calcium supplements** ± bisphosphonates at baseline (n=124)				
	Baseline	24.2	59.7	16.1	
	At 1 year	43.6	54.0	2.4	<0.001
	At 2 years	70.2	29.8	0	<0.001
RF	Without calcium supplements** ± bisphosphonates at baseline (n=226)				
	Baseline	97.8	2.2	0	
	At 1 year	34.5	63.3	2.2	<0.001
	At 2 years	76.5	23.4	0	<0.001
	With calcium supplements** ± bisphosphonates at baseline (n=124)				
	Baseline	21.0	63.7	15.3	
	At 1 year	36.3	61.3	2.4	<0.001
	At 2 years	68.5	31.5	0	<0.001

**Calcium with Vitamin D supplements. BMD=Bone mineral density, LF=Left femur, RF=Right femur

2 years (−5.3% and −3%). This may be because majority of our patients (92%) were using letrozole which is a more potent estrogen suppressant as compared to exemestane.^[5] In the ARIBON trial,^[21] after 2 years of therapy with anastrozole, the mean percentage change in BMD at LS and total hip was −4.79 and −3.72, respectively. At 1 year, BMD loss at LS was less compared to BMD loss observed in our study. The BMD loss detected in SABRE trial^[22] was much less compared to ARIBON study because all the breast malignancy patients in SABRE trial were prescribed Vitamin D and calcium along with anastrozole from baseline. This indicates that calcium and Vitamin D supplements also have a beneficial effect on BMD; however, in our study, only 18.3% (64/350) of patients were prescribed calcium and Vitamin D supplements [Table 3] along with AIs from baseline and they had a significant gain in mean BMD at 1 year. In the NCIC CTG MA.17 bone substudy,^[23] with a median follow-up of 2 years, women who received letrozole compared to placebo had a higher BMD reduction at LS (−5.35% vs. −0.7%) and total hip (−3.6% vs. −0.71%) in spite of the fact that they received 5 years of tamoxifen in the premenopausal phase. In our study, 2 years after initiation of supportive therapy, there was a significant gain in % mean BMD but those who received supportive therapy from baseline, there was significant elevation in % mean BMD at 1 year as well as at 2 years. Hence, our findings indicate that all the patients should be initiated on supportive therapy along with AIs. Data regarding BMD measurements at RF and LF are not available in the previous studies or trials^[24-27] but have observed the effect of AIs on LS and total hip BMD as compared to tamoxifen which has a bone protective effect.

Brufsky *et al.*^[28] have shown that bisphosphonates, with adjuvant AI therapy, in breast neoplasm patients are effective and safe in preventing BMD loss with IV zoledronic acid as

the bisphosphonate with proven efficacy for the prevention of AIBL. Another clinical trial^[26] ABCSG-12 has also shown elevation of BMD when AIs were given with IV zoledronic acid in PMW with breast malignancy. ABCSG trial indicates that endocrine therapy for 3 years without zoledronic acid led to significant bone loss by 11.3% at LS whereas addition of zoledronic acid increased BMD by 4%. Benefit of IV zoledronic acid is that it can bypass the disadvantages, such as gastrointestinal intolerance, inadequate compliance, and poor bioavailability of orally administered bisphosphonates.^[29] Even though other bisphosphonates may also be equally effective, parenteral zoledronic acid was the only bisphosphonate used (off-label) in our patients.

In our study, at 1 year, addition of supportive therapies along with AIs in all the patients led to significant gain in BMD of LS and dual femur at 2 years of BMD monitoring. Although the increase was significant at 2 years, their BMD did not reach the baseline level. Significantly greater % elevation in mean BMD was observed in patients who received a combination of calcium supplements and bisphosphonates along with AIs as compared to those receiving AIs with calcium and Vitamin D supplements only [Table 3]. Hence, bisphosphonates with calcium and Vitamin D supplements will be a better choice for AIBL.

TEAM trial,^[24] a multicenter study, showed that majority of patients with normal BMD at baseline treated with exemestane became osteopenic at 1 year although only one patient became osteoporotic. Osteoporosis or osteopenia was identified in our study patients based on T-score of LS and dual femur. Our study also showed significant increase in fracture risk as most of the patients (74.8%, 169/226) became osteopenic and 25 (11%) new cases of osteoporosis

developed at 1 year due to AI monotherapy. However, with the addition of supportive therapies, there was significant change in fracture risk of patients and majority of osteopenic patients attained normal BMD and osteoporotic patients became osteopenic [Tables 4 and 5]. Our findings suggest that Z-score of the patients receiving AIs does not get affected as much as the T-score. This may also be the reason for the nonavailability of previously published literature regarding Z-score. After 5 years of follow-up, ATAC trial^[25] has shown significant elevation in the incidence of fractures in patients receiving AIs (11%) compared to tamoxifen (7.7%). However, in our study, the incidence of fractures was less (1.1%) and observed only in patients >70 years old who were not initiated on supportive therapies at baseline. At 1 year, all the patients were prescribed supportive therapies, and therefore, further cases of fractures were not seen.

As per the ASCO guidelines,^[11] patients with T-score <-2 should be initiated on bisphosphonates plus calcium and Vitamin D supplements and those with T-score ≥-2 should be initiated on calcium and Vitamin D supplements along with AI from the baseline. However, majority of our patients (64.6%) were prescribed neither calcium and Vitamin D supplements nor calcium supplements and bisphosphonates at baseline. After the loss of BMD at 1 year, majority of our patients received calcium and Vitamin D supplements which helped them to maintain BMD within relevant limits, and the increase in BMD persisted at 2 years of BMD measurement. Hence, our study strengthens the evidence for adequate intake of calcium and Vitamin D supplements and regular monitoring of BMD by DEXA scan in all patients receiving AI right from the baseline. In our patients who were not given supportive therapies had a normal BMD at baseline, this may be the reason why they were not initiated supportive therapies. The key message of our study is that even those who have normal BMD at initiation of AIs should be provided with supportive therapies, such as calcium and Vitamin D supplements to prevent AIBL and consequent risk of fracture. Our findings recommend that patients intending to receive AI therapy should be informed about risk factors of fractures as well as monitoring of BMD at baseline and annually and also about taking supportive therapy for the prevention of AIBL. For all patients started on AI therapy, fracture risk should be assessed by BMD measurement and FRAX tool and patients at risk of bone loss should be identified and managed based on clinical guidelines.

CONCLUSION

AIs can result in significant loss of LS and dual femur BMD at 1 year from baseline in patients not initiated on calcium and Vitamin D supplements, but significant improvement in BMD can occur at 2 years with the addition of calcium and Vitamin D supplements ± bisphosphonates (parenteral zoledronic acid). AIs with supportive therapy at baseline can cause significant gain in BMD at 1 year, and this gain in BMD can persist at 2 years. Since the increase in BMD was significantly greater

with bisphosphonates as compared to supportive therapy with calcium and Vitamin D supplements, bisphosphonates are a better choice for AIBL as compared to calcium and Vitamin D supplements. We would recommend that all postmenopausal breast cancer patients who are intended to be started on aromatase inhibitors, irrespective of their baseline bone density parameters, should be concurrently advised bone supportive measure with bisphosphonate, calcium and Vitamin D. This should be supplemented with bone health education and annual surveillance of BMD.

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Conflicts of interest

There are no conflicts of interest.

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