Effect of aromatase inhibitors on bone densitometry and microarchitecture assessed by trabecular bone score in breast cancer

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ABSTRACT

Introduction: During treatment of hormone-receptor positive breast cancers, Aromatase inhibitors (AIs) are commonly used. However, AIs are recognized to induce bone density loss and increase the risk of fractures. Recently, trabecular bone score (TBS) has been introduced to assess bone microarchitecture. Our study aimed to investigate changes in bone mineral density (BMD) and TBS in breast cancer patients treated with AIs.

Methods: Fifty-one patients with a mean age 59.75 ± 10.95 and a pathology-proven diagnosis of breast cancer underwent bone mineral densitometry (BMD) using the DXA method. BMD and TBS were recorded before and 6 months after starting treatment with AIs.

Results: By comparing the bone density measurements before and six months after starting treatment with AIs, we observed a significant decrease in bone density in the lumbar region and total hip, but no significant change in TBS. Additionally, when comparing the TBS-adjusted 10-year risk probability of major osteoporosis and hip fracture (FRAX) before and six months after starting the medication, we found no statistically significant difference between the two time points.

Conclusions: This study examined bone density and T-score in the lumbar region and total hip in breast cancer patients treated with aromatase inhibitors (AIs). The results show a clear reduction in bone density after 6 months of treatment, which lead to an increased risk of fracture in these patients. Notably, TBS, FRAX and even FRAX adjusted with TBS do not exhibit significant changes over this short-term period.

Keywords: Breast cancer; Aromatase inhibitors; Bone mineral densitometry; Trabecular bone score

INTRODUCTION

Breast cancer patients are generally at a higher risk of bone loss and fractures due to multiple factors. One key factor is the physiological decline in estrogen levels after menopause, which contributes to reduce bone mineral density (BMD) and increases fracture risk [1-5]. Additionally, aromatase inhibitors (AIs), commonly used to treat hormone receptor-positive breast cancer, exacerbate bone loss by suppressing peripheral oestrogen production. This leads to more significant decline in estrogen levels than typically observed in postmenopausal women, causing a greater loss of bone density and a heightened risk of osteoporotic or fragility fractures.

The National Comprehensive Cancer Network (NCCN) Task Force recommends evaluating and screening fracture risk in all patients who are starting aromatase inhibitors (AIs) using BMD measurements and the FRAX® calculator [6-16]. In recent years, research has revealed that the increased risk of non-traumatic fractures associated with low bone density is influenced not only by the mineral content of bones but also by the quality and the microarchitecture of trabecular bone.

The Trabecular Bone Score (TBS) as a bone microarchitecture index is a new tissue textural parameter that is derived from lumbar spine DXA images and reflects the microscopic changes in bone structure, measuring trabecular characteristics and microscopic changes of the skeleton. A high TBS is associated with dense, well-connected, and fracture-resistant bone microarchitecture. When combined with Bone Mineral Density (BMD), TBS is believed to enhance the identification of patients at risk for fractures [17-31]. This study was designed to *assess* the effects of AIs on BMD and TBS during the AI treatment in patients with breast cancer.

METHODS

Patients with a confirmed diagnosis of breast cancer who underwent mastectomy or breast-conserving surgery were referred to the oncology department by a surgeon or oncologist for further treatment. Patients who had indications for starting treatment with an AI alone were selected. The exclusion criteria were a history of bone diseases, osteoporotic fractures, spine or femur surgery, endocrine or metabolic diseases, Paget's disease, osteomalacia, rheumatoid arthritis, smoking, alcohol consumption, or the use of bisphosphonates, corticosteroids, or any other bone-active medications. Patients who had previously received neoadjuvant chemotherapy or were currently receiving chemotherapy were excluded. Additionally, patients with a BMI greater than 37 were excluded because the Trabecular Bone Score (TBS) has not been validated in this population.

Another important point was the intake of vitamin D and calcium, which all patients routinely used. Also, it is necessary to mention that short-duration surgery (such as mastectomy or breast-conserving surgery) is unlikely to have a significant long-term effect on BMD and therefore was not considered ~~as~~ an exclusion criterion.

The study was approved by the local ethics committees.

Then the patients were referred to the nuclear medicine department for bone density measurement. Patients were verbally informed about the purpose and necessity of the study, and then completed the consent form.

The patients underwent bone mineral densitometry from two areas of the lumbar spine and proximal femur and TBS measurement. BMD was measured based on the DXA method using Hologic discovery device. TBS and FRAX® score (both with and without TBS adjustment) were calculated. The FRAX® score was calculated using clinical data from patients' charts. Bone Mineral Density (BMD) was assessed based on World Health Organization (WHO) guidelines, which classify fracture risk according to the T-score. The T-score represents the

standard deviation difference between a patient's BMD and that of a young adult reference population. Systemic treatment with an aromatase inhibitor (letrozole, fixed dose, once daily) was started for the patient. After six months from the start of treatment, the bone density measurement was repeated, and these parameters were recalculated.
Lastly, changes in BMD, TBS, and FRAX® scores before and after six months of AIs treatment were assessed. No patient underwent chemotherapy or radiation therapy during the six-month period of Als use between the two BMD measurements.

Statistical analysis
The information recorded in the checklist included demographic information. Descriptive statistics were reported as means and standard deviations and presented in tables. It should be mentioned that the data of age, weight and body mass index before and after treatment had a normal distribution according to the Shapiro-Wilk test. Kolmogorov-Smirnov test ascertained normal distribution of data. Statistical analysis was performed using IBM Statistical Package (SPSS). Statistical analysis was performed using a paired T-test. P values less than 0.05 were considered significant.

RESULTS
In the upcoming research, 51 patients with breast cancer who were candidates for treatment with AIs were included in the study. The average age of these people was 59.75 ± 10.95 (38 to 85 years). Demographic and clinical characteristics are summarized in Table 1.
Table 2 shows weight, body mass index, BMD, TBS, and FRAX® variables at baseline and after 6 months of AI therapy.
Aromatase inhibitor (AI) therapy was associated with statistically significant declines in lumbar spine and left total hip BMD (g/cm^2), while no significant changes were observed in femoral neck BMD. Similar trends were noted in the T-scores. No notable changes were observed in the Trabecular Bone Score (TBS) or in the calculated FRAX® 10-year probability of a hip fracture or a major osteoporosis-related fracture, both with and without TBS adjustment.

DISCUSSION
Our study revealed a decline in lumbar and total hip T-scores and BMD after 6 months of AI therapy, whereas TBS, FRAX variables, and TBS-adjusted FRAX variables remained relatively stable. While BMD is the standard method for detecting osteopenia and osteoporosis, it has limitations. BMD primarily reflects cortical bone density (constituting ~80% of bone volume), with a relatively low turnover rate, and may not capture changes in trabecular bone microarchitecture, potentially underestimating structural alterations [31].
The FRAX® tool is the most extensively validated method for calculating fracture risk, combining BMD with clinical risk factors. In the context of aromatase inhibitor (AI) therapy, FRAX® aids in determining whether to initiate bone-modifying agents (BMAs) in women with borderline BMD (osteopenia). A substantial body of evidence supports the utility of the Trabecular Bone Score (TBS) in predicting fragility fractures. Consistent with previous findings, the impact of AI therapy on TBS did not appear to correlate with changes in BMD. This suggests that TBS and BMD assess complementary aspects of fracture risk and could potentially be combined to provide a more sensitive measure of bone fragility.
In this study, the bone density of the lumbar region was significantly reduced with aromatase inhibitor treatment, which was similar the results of previous studies conducted in this field.
In a retrospective study conducted in 2017, the authors reported with a follow-up of more than 18 months, patients had significant changes in TBS. In another study conducted by Catalano et

al. in 2019, TBS was significantly reduced after 18 months of AI therapy. The follow-up time in this study was much longer than our study time [32].
Pedrazzoni et al. reported that after an average follow-up of 2.9 years, decrease in BMD and TBS with consumption of AI was more prominent than in menopausal women [33].
In a prospective study, patients who did not take bisphosphonates had a clear decrease in BMD of the lumbar region, and TBS also decreased significantly, but in patients treated with bisphosphonates, lumbar BMD increased and TBS remained unchanged. The obvious difference in this study was that TBS and BMD were re-examined after the end of the 5-year treatment period [31].
Our study found that bone density in the lumbar region and total hip declined significantly after 6 months of AI therapy, while TBS and FRAX variables, including TBS-adjusted FRAX, showed no remarkable changes. The decline in TBS was not statistically significant, possibly due to the short follow-up period. Longer-term follow-up may reveal a correlation between TBS decline and prolonged AI use. Serial TBS assessments may help identify individuals at increased risk of fractures.
The rapid decline in BMD and T-scores, compared to TBS and FRAX, suggests that BMD is a more sensitive indicator of early bone changes. FRAX and TBS changes are slower, likely due to their dependence on clinical variables and bone microarchitecture factors.
These findings highlight the importance of early monitoring and follow-up for breast cancer patients on AI therapy, particularly with BMD assessments. This study's results can inform larger studies and contribute to developing national guidelines for improving the quality of life of these patients.

Study limitations

This study's limitations include a short 6-month follow-up period, which may not capture the full extent of bone changes. However, the findings confirm the slow rate of change in TBS over time. Additionally, the study's small sample size (n=51) was challenging to achieve due to numerous confounding variables. A longer follow-up period and larger sample size would provide a more comprehensive understanding of trabecular bone score changes.

CONCLUSION

According to this study, bone density and T-score in the lumbar region and total hip in breast cancer patients treated with AIs are clearly reduced after 6 months of treatment and lead to an increased risk of fracture in these patients. However, TBS, FRAX® and even FRAX® adjusted with TBS do not change quickly. They change more slowly than BMD and T-Scores.

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Table 1. Demographic and clinical characteristics of the study population

Vitamin D and Calcium supplements		100%
Hysterectomy and BSO		20%
Cancer Variation	Invasive ductile carcinoma	44%
	Invasive lobular carcinoma	0%
	Ductal carcinoma in-situ	7%
Side involved	Right	35%
	Left	16%
Type of surgery	Lumpectomy	10%
	Partial mastectomy	2%
	Modified radical mastectomy	39%
	Mastectomy	0 %
Chemotherapy		33%
Radiotherapy		36%

BSO: Bilateral salpingo-oophorectomy

Table 2. Trends in BMD, organized by clinical and demographic characteristics of patients

	BMD, Baseline	BMD, after 6 months	p value
Weight (kg)	73.01±10.45	71.99±10.89	0.561
BMI (kg/cm2)	29.22±3.91	28.99±4.08	0.701
LS BMD (gr/cm2)	1.02±0.16	1.01±0.15	0.005
FN BMD (gr/cm2)	0.88±0.15	0.87±0.14	0.227
TH BMD (gr/cm2)	0.95±0.13	0.94±0.13	0.017
LS T-score	-1.46±0.19	-1.65±0.52	0.001
FN T-score	-1.37±0.52	-1.25±0.46	0.345
TH T-score	1.09±0.16	-0.99±0.14	0.003
TBS	1.37±0.12	1.36±0.14	0.885
10-year risk of major osteoporosis (%)	4.14±1.84	4.54±2.18	0.149
10-year risk of hip fracture (%)	0.79±0.77	0.84±0.75	0.799
10-year risk of major osteoporosis adjusted with TBS (%)	4.51±2.24	5.24±2.51	0.125
10-year risk of hip fracture adjusted with TBS (%)	0.88±0.73	0.92±0.79	0.547

LS: lumbar spine; FN: Femoral neck; TH: total hip; BMD: Bone mineral density; TBS: Trabecular bone score