Bone Mass Loss in Postmenopausal Women with Early-Stage Breast Cancer (I, II, III) Treated with Aromatase Inhibitors

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ABSTRACT:

BACKGROUND:

Adjuvant hormonal treatment with aromatase inhibitors for postmenopausal women with early-stage breast cancer is associated with relatively few side effects but it may cause bone mass loss which can be detected with a dual-energy x-ray absorptiometry scan.

AIM:

In this study, we evaluate the skeletal effects of aromatase inhibitors in postmenopausal women with early-stage breast cancer.

PATIENTS AND METHODS:

This is an observational retrospective case-control study enrolled 70 postmenopausal women with early-stage breast cancer on adjuvant aromatase inhibitors and 70 postmenopausal control women, the two groups were compared regarding the prevalence and severity of bone mass loss by using the DXA scan of their lumbar spine.

RESULTS:

Bone mineral density was significantly lower in breast cancer cases (mean T score was (-2.50 ± 1.01) compared to the control group (mean T score was (-2.12 ± 0.79) with significant (p-value =0.014), also 60% of breast cancer cases were osteoporotic compared to **32%** in the control group (p-value =0.005). Based on univariate analysis, breast cancer was associated with **2.79 folds** increased probability of osteoporosis

CONCLUSION:

A significant proportion of our breast cancer patients who used aromatase inhibitors were osteoporotic.

KEYWORDS: DXA, osteoporosis, aromatase inhibitors.

INTRODUCTION:

Breast cancer remains the most common malignancy diagnosed among women in the world, with about 1.7 million women worldwide diagnosed in 2012, accounting for 25% of all new cancer cases. [(1)]

Estrogens play a role in breast cancer risk and development. Increased levels of premenopausal endogenous hormones are associated with an increased risk of developing breast cancer among postmenopausal women. [(2)]

Definition of postmenopausal state: (Menopause is defined as age > 60 years, women < 60 years with spontaneous cessation of menses > 12 months, women with bilateral oophorectomy, or women < 60 years with no spontaneous menses for < 1 year but with postmenopausal estradiol levels. (3)

Although tamoxifen works by binding to the ER, aromatase inhibitors (AIs) act through inhibition of the aromatase enzyme that converts androgens into estrogens resulting in profound estrogen depletion, thereby leading to an accelerated bone loss and an increased fracture risk. [(4)]

Aromatase inhibitors (AIs) are not appropriate for premenopausal patients, as residual ovarian function can lead to enhanced production of aromatase and thus overcome the effects of AIs. [(5)]

Although AIs. treatment has clear benefits for patients with breast cancer by increasing their disease-free survival and decreasing their risk of recurrence , they adversely affect bone health accelerate bone turnover and result in decreased bone mineral density (BMD), have a twofold higher risk of fracture in patients with breast cancer compared to healthy postmenopausal women .[(6)]

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The commonest short-term effects of AIs are hot flashes, vaginal dryness, musculoskeletal pain, and headache, but they are usually mild. [7] The third-generation AIs (like the letrozole and Armidex) appear to be very well tolerated,[8] Comparative trials indicate that such adverse effects are very similar in nature and frequency to those of tamoxifen .[9]

Normally the maintenance of bone density depends in part on estrogen. Tamoxifen reduces bone demineralization through its agonist effect with estrogen, at least in postmenopausal women, whereas aromatase inhibitors may enhance this process by lowering circulating estrogen levels. Short-term use of letrozole (an AI) is associated with an increase in bone-resorption markers in plasma and urine, and the adjuvant therapy with AIs. appears to be associated with significant bone loss. However, it is possible that prevented or modified with concurrent use of bisphosphonates.[10]

In premenopausal women, cancer treatment-induced bone Loss (CTIBL) could be caused by various mechanisms such as early direct negative effect of chemotherapy and corticosteroids on bone and indirect effect of chemotherapy-induced amenorrhea. It can also be caused by chemotherapy with resultant ovarian failure, by gonadotropin - releasing hormone (GnRH) agonist (e.g., Lupron, goserelin) or by tamoxifen. Chemotherapy-induced ovarian dysfunction accelerates the onset of menopause by an average of 10 years. [11]

Several non-invasive techniques are available for estimating skeletal mass or density. They include dual-energy x-ray absorptiometry (DXA), single energy x-ray absorptiometry (SXA), quantitative CT, and ultrasound (US), and recently the MRI technique and trabecular bone scan (TBS). [12]

DXA scan is a highly accurate x-ray technique that has become the standard tool for measuring bone density in most centers. Though it can be used for measurement in any skeletal site, clinical determination usually are made of the lumbar spine and hip, using T-scores, which compare individual results to those of normal young population that is matched for race and sex. Z-scores compare individual results to those of an age-matched population in addition to race and sex. **(13).**

T score is interpreted as follows: **(14).**

T≥ -1: normal
T -2.5_ -1: osteopenia
T≤ -2.5: Osteoporosis
T≤ -2.5 with fragility fracture: Established osteoporosis

PATIENTS AND METHOD:

This is an observational retrospective case-control study conducted from (April 1st /2017 to (October 1,st 2017) to study the prevalence and severity of bone mass loss in postmenopausal women with early-stage breast cancer (stage I , II, and III) treated with AI hormonal therapy.

Our study included two groups of patients, the first group(the case group) composed of 70 postmenopausal women with early-stage breast cancer on adjuvant hormonal treatment with AI (armedex or literizol) for at least six months at Oncology Teaching Hospital /Baghdad Medical City and were sent for DXA scan of the lumbar spines**.** The second group (the control group) included other 70 postmenopausal women patients from rheumatology unit/Baghdad teaching hospital who visited rheumatology unit for non-specific symptoms and for whom DXA scan of the lumber area was ordered to them by their rheumatologist

We excluded patients with lumbar spine trauma, or a history of non-traumatic fractures, and those who had received recent treatment with drugs known to affect the skeleton, like steroid or bisphosphonate, and patients with diseases known to influence bone like renal dysfunction, diabetes mellitus, uncontrolled bronchial asthma , rheumatoid arthritis.

Both groups were compared regarding their bone mineral density (BMD) loss, and grouped into normal, osteopenia or osteoporosis, using DXA scan of their lumbar area and assessed with DXA machine type (STRATOS-DMS / Turkish mode/France).

Statistical analysis:

Discrete variables presented as number and percentage, chi-square test was used for analysis whenever applicable, and two samples t-test was used to analyze differences in means of two groups, binary logistic regression analysis was used to calculate the odd ratio (OR) and their 95% confidence intervals, ordinal logistic regression analysis used for finding the relationship between (bone status) with other variables, SPSS 20.0.0,

Minitab 17.1.0 software package used to make the statistical analysis, p-value< 0.05 was considered significant.

RESULTS:

Both studied groups were age and BMI matched (table 1.) and there was no significant difference in bone status (normal, osteopenia, and osteoporosis) to the stage of the disease (table 2).

Table 1: Demographic patients' characteristics of women in both groups.

Variables	Control group	Case group	P* value
Number	70	70	-
Age (years)	59.36 ± 6.91	58.53 ± 5.65	0.439
BMI (kg/m^2)	32.79 ± 5.62	33.05 ± 6.44	0.805
Duration of AI	-	22.06 ± 13.22	-

The current study shows that stage II breast cancer has the highest proportion (60%) among the 70 breast cancer cases, also our study shows that the disease stage has no significant effect on bone status as illustrated in table 2.

Table 2: Association between bone status and staging in BC patients.

Stages	Normal	Osteopenia	Osteoporosis	Total	P-value*
Number	3	25	42	70	-
Stage I	0 (0.0%)	2 (8.0%)	4 (9.5%)	6	0.953
Stage II	2 (66.7%)	17 (68.0%)	25 (59.5%)	44	
Stage III	1 (33.3%)	6 (24.0%)	13 (31.0%)	20	

*Chi-square test

These results were consistent with the statistical results obtained by Fraenkel M. et al. study which did not find any association between BMD at any of the skeletal sites and breast cancer stage, histology, or grade. (15)

T score was significantly lower in BC cases compared to control, and osteoporosis occurred in 60% of breast cancer compared to 32.9% in control (table 3), and the use of AI for more than 12 months was associated with a significantly more severe bone loss compared to those used it for less than 12 months as shown in table 5.

Table 3: T score of the breast cancer patients and the control groups.

Variables	Control	Breast cancer	P-value
Number	70	70	
Mean T score	-2.12 ± 0.79	-2.50 ± 1.01	0.014*
Normal	3 (4.3%)	3 (4.3%)	
Osteopenia	44 (62.9%)	25 (35.7%)	
Osteoporosis	23 (32.9%)	42 (60.0%)	0.005
Total	70	70	

* t-test

Based on multivariate analysis, the study showed that both advanced age and breast cancer were found to be independent predictors for osteoporosis as shown in table 4.

Table 4: Ordinal regression analysis of the predictors of osteoporosis.

Predictors	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P-value	OR (95%CI)	P-value
Breast cancer	2.790(1.423-5.471)	0.003	3.057(1.527-6.118)	0.002
Age	1.063(1.008-1.121)	0.023	1.073(1.015-1.133)	0.012
BMI	0.992(0.939-1.048)	0.774	-	
Omnibus test: Likelihood ratio = 15.757, p <0.001				

Duration of AIs is also shown to be a risk factor for osteoporosis with a significant p-value as shown in table 5.

Table 5: Duration of Aromatase inhibitors treatment and bone status.

Duration of AI	Normal	Osteopenia	Osteoporosis	Total	P-value
Number	3	25	42	70	-
<12 months	1(33.3%)	9 (36.0%)	5 (11.9%)	15	0.037
≥12 months	2(66.7%)	16 (64.0%)	37 (88.1%)	55	
	Chi-square test, bootstrapping was performed using 1000 resample				

DISCUSSION:

The present study was designed to estimate the prevalence and severity of bone loss among 70 postmenopausal female patients with early-stage breast cancer using adjuvant AIs for at least 6 months compared to other age-matched 70 control patients.

Our study showed no significant effect of disease stage and bone loss consistent with results obtained by Fraenkel M. et al. study [15] which did not find any association between BMD at any of the skeletal sites and breast cancer stage, histology, or grade.

On the other hand, a significant increase in bone loss was found in patients treated with AIs. The mean T score of the control group was in the osteopenia range (-2.12 ± 0.79), compared to (-2.50 ± 1.01) in the osteoporosis range, with a significant P-value of (0.014). 60% of breast cancer patients were in the osteoporosis range compared to 32.9% of the control group (p-value = 0.005), comparable to results obtained by Hadji P. trial[16] showing AI-induced bone loss is two times more than that of physiologic postmenopausal bone loss.

The current study is based on multivariate analysis, both advanced age and breast cancer were found independent predictors for osteoporosis. Breast cancer is associated with 3.057 folds increase in osteoporosis [95% confidence interval (CI), 1.527- 6.118, with significant P-value=0.002] and the advanced age was associated with 1.073 folds increase in osteoporosis [95% confidence interval (CI), 1.015-1.133,) with significant P-value =0.012, finding consistent with those of Kohlmeier and Lynn Kohlmeier (1998)[17]

Duration of AIs is also shown to be a risk factor for osteoporosis, with about (11.9%) of the total osteoporotic breast cancer patients having duration of exposure to AIs for less than 12 months, compared to (88.1%) of the osteoporotic breast cancer patients had a duration of at least 12 months, with a significant P-value of (0.037). a finding consistent with that of Eastell R. et al. [18] study that shows osteoporosis increase with prolonged duration of exposure to AIs therapy from 1% annually in natural menopause women to about **2%** in women on AIs.

CONCLUSIONS and RECOMMENDATIONS:

Breast cancer patients were associated significantly increased probability of osteoporosis making routine baseline DXA study followed by regular follow-up is advisable.

Duration of treatment with adjuvant AIs of 12 months and more was significantly associated with a high risk of BMD loss-making more often DXA study is advisable.

The benefit of the anti-resorptive therapy started in the early-stages of breast cancer on adjuvant AIs. need to be studied.

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