IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 14, Issue 7 Ver. IV (July. 2015), PP 61-66
www.iosrjournals.org

Prevalence and Predictors of Low Bone Mineral Density in Iraqi Patients with Breast Cancer: A Cross Sectional Study

Ziad S. Al-Rawi[1], Faiq I. Gorial [1], ManwarAbdulelahAlnaqqash[2], Russul Hakim Al-Salami [3]

[1] *Department of Medicine, College of Medicine, Baghdad University, Baghdad, Iraq*
[2]*Department of Oncology, College of Medicine, Baghdad University, Baghdad, Iraq*
[3] *Baghdad Teaching Hospital, Rheumatology Unit, Baghdad, Iraq*

Abstract:
Background: *Bone mineral density (BMD) is a standard measure for the diagnosis of osteoporosis and assessment of fracture risk. Breast cancer (BCA) itself may increase osteoclastic activity and subsequently enhancing bone resorption*
Objective:*To assessthe prevalence and predictors of low BMD in Iraqi patients with BCA.*
Patients and methods: *A total of (100) Iraqi patients with BCA (99 females & 1male) diagnosed according to clinical examination, breast imaging, and cytological examination were included in the study. A questionnaire form consisted of personal data, breast cancer related data, fracture risk assessment using the FRAX tool and joint mobility. Compete blood picture, erythrocyte sedimentation rate (ESR), C- reactive protein, serum calcium, serum phosphorus, serum alkaline phosphatase, and parathyroid hormone were done for each patient BMD was measured using dual X-ray absorptiometry (DXA) machine at lumbar spine and right femur.*
Results: *At the femur neck, the prevalence of osteopenia was 29% and that of osteoporosis was 23%, while at lumbar spine, 39% of patients had osteopenia and 26% had osteoporosis. Old age patients, advanced age at menopause (early menopause), FRAX score & increased CRP were significant predictors for low BMD at the spine. Old age of patient, advanced age at menopause (early menopause), increased joint mobility Score & FRAX score were significant predictors for low BMD at femur neck.*
Conclusions:*Low BMD was common in Iraqi BCA survivors. Older age females, high FRAX score, increased joint mobility score and increased levels of CRP were significant associates with low BMD, while advanced age at menopause was protective.*
Keywords:*Breast cancer, bone mineral density, Dual X-ray absorptiometry.*

I. Introduction

Breast cancer (BCA) is a type of cancer originating from breast tissue, most commonly from the inner lining of milk ducts or the lobules that supply the ducts with milk [1]. In 2008 breast cancer caused 458.503 deaths worldwide (13.7% of cancer deaths in women) [2]. A large proportion of women are diagnosed with breast cancer during the menopausal transition or in the menopause [3].Osteoporosis has become a global public health problem that is estimated to affect more than 200 million people worldwide [4]. In Iraq, high prevalence of osteoporosis in Iraqi postmenopausal women (22.8 %) according to one recent study [5].

In BCA survivors ovarian failure resulting from chemotherapy or the reproductive aging process is associated with decreased bone density [3,6]. BCA patients > 40 years of age are more likely to develop amenorrhea after chemotherapy than younger women with rapid bone loss and bone loss starts to accelerate 2 years after menopause. In addition,some authors have suggested that a decrease in BMD may occur in BCA survivors undergoing chemotherapy irrespective of the effect of chemotherapy on ovarian function.Osteoclastic activity may increase from BCA itself, enhancing bone resorption [7,8]. Most studies investigating BMD in BCA survivors were conducted in developed countries [9, 10].This study aimedto assess the prevalence and predictors of Low BMD in Iraqi patients with breast cancer patients.

II. Patients and Methods

Study design

We conducted a cross- sectional study on a sample of (100) Iraqi BCA patients during their visit to the oncology & rheumatology units in Baghdad Teaching Hospital from June 2013 to June 2014.

Sample selection

A total of 100 consecutive Iraqi patients with BCA were included in this study regardless of menopausal state for the female patients and type of cancer treatment received.Patients with comorbid diseases

and other tumors were excluded from the study.Diagnosis of BCA was made according to the triple diagnostic investigations [11] which includedclinical breast examination, breast imaging: ultrasonography or mammography, and cytopathologic or histopathologic finding.Informed consent was obtained from each participant included in this study. Ethical approval was obtained from the Ethics Committee of Baghdad University, College of Medicine, Medical Department.

Clinical, laboratory, and imaging evaluation

A questionnaire form consisted of 1) Personal data: Age, sex, Body Mass Index (BMI), joint mobility according to Beighton score [12]. History of smoking, and for female patients; age of menarche, menopausal state, age at menopause, years since menopause and parity. 2) BCA related data: time since BCA diagnosis, tumor stage & cancer treatment with chemotherapy, radiotherapy, and others.Fracture risk assessment (FRAX) for the % ten-year probability of majorosteoporotic and hip fractures respectively, was calculated using theFRAX tool developed from a Swedish cohort. The FRAX tool appliesonly to patients 40 years or older. The probability was calculated using known risk factors for fractures, and BMD of the femoral neck [13].

Serum calcium, serum phosphorus, serum alkaline phosphatase, and parathyroid hormone as well as complete blood picture, erythrocyte sedimentation rate (ESR) and C-reactive protein were done for each individual. Vitamin D measurement was not conducted due to the lack of this test in our labs. For all our patients the BMD measurement was performed using DXA machine (Dexxum 3 OSTEOSYXS-Made in Korea) and we obtained BMD values at lumbar spine (L1-L4) and the right femur. We requested DXA left femur however they did not measure it for technical reasons.Diagnostic criteria for osteoporosis were based on information from the National Osteoporosis Foundation (NOF) 2008. T score between +1 to -1 standard deviation is normal, -1 to -2.5 standard deviation is low bone mass, and -2.5 standard deviation or lower is osteoporosis [14].

Statistical analysis

Data of the studied group were entered and analyzed by using the statistical package for social sciences (SPSS) version 21. Descriptive statistics were presented as mean, standard deviation (SD), frequencies (Numbers) and percentages (%).Multiple logistic regression tests (enter model, binary) was used to assess the correlation between low BMD at femur neck or spine with other variables, and to estimate the more predictive values of these predictors.Level of significance of < 0.05 considered significant, finally results and findings were presented in tables and figures with explanatory paragraphs.

III. Results

A total of 100 patients enrolled in this study with a mean age of (52.3 ± 8.2) years, Females were dominant; 99 (99%) vs. only one male (1%). The mean BMI was 30.3 ± 3.7 kg/m^2.Eight patients (8%) had stage 1, 28 patients (28%) stage 2, 40 patients (40%) stage 3, and 24 patients (24%) stage 4. Other characteristics of the study group were shown in table 1.

The prevalence of low BMD at the total femoral neck was (54.0 %). Of those, 31 patients (31%) had osteopenia and 23 patients (23%) had osteoporosis. At the right femoral neck the prevalence of low BMD was (52%). The prevalence of osteopenia and osteoporosis was (29%) and (23%), respectively. At the lumbar spine (L2-L4), the prevalence of low BMD was (65%). Of those osteopenia was (39%) and osteoporosis was (26%). Generally, the prevalence values were higher in lumber spine than femoral neck sites (Fig. 1).

To assess the correlation between the low BMD and other characteristics and to find the predictors of low BMD, a multiple logistic regression (Binary model) was performed, according to the T-score, BMD categorized either normal or low (binary), and correlated with different variables. For the predictors of low BMD at spine, multiple logistic regression revealed that old age of patient, advanced women age at menopause (early menopause), FRAX % (score) for major osteoporotic fracture at any site, and CRP were significant predictors for low BMD at spine (Table 2).

At the spine, we found a direct (positive) significant correlation between the low BMD and: the age of patient (Odds ratio= 1.3, P< 0.001) [indicating that elderly were more likely to have low BMD] and FRAX % (score) for major osteoporotic fracture at any site (OR=1.3, P=0.006). However, Low BMD appeared to be inversely (negatively) correlated with: advanced age at menopause; women with advanced age at menopause were less likely to have low BMD at spine (OR=0.25, P<0.001), and with positive CRP (OR=0.14, P=0.001).The comparison of odds ratio for these significant predictors detected that age of patients was the stronger predictor, followed by FRAX % (score) for major osteoporotic fracture at any site, age at menopause, and then the positive CRP.

The correlation of low BMD with other variables didn't reach the statistical significance (P>0.05).In addition, the correlation between low BMD at femur neck with other variables, old age of patient, advanced age

at menopause, joint mobility and FRAX % score for fracture hip appeared to be significant predictors for low BMD as shown in table 3.

The patients age showed a direct significant correlation with low BMD (OR=5.2, P<0.001) which indicated that elderly patients were about 5 folds more likely to have low BMD than younger patients. Regarding the joint mobility, it had been significantly found that patients with joint mobility were about 7 folds more likely to have low BMD (OR=7.2, P=0.014) Also patients with higher FRAX % score for fracture hip were about 1.4 folds more likely to have low BMD (OR=1.41, P=0.005) as shown in table 3.

The advanced age of women at menopause was inversely correlated with the low BMD; women with advanced age at menopause were less likely to have low BMD than women with younger age at menopause (OR=0.35, P<0.001, table 3).

According to these findings and by comparing the odds ratio of these 4 significant predictors, we found that joint mobility appear to be the strongest predictor of low BMD (the highest odds ratio), followed by age of the patient, FRAX % score for fracture hip, and the least predictor was the women age at menopause.

The correlations between low BMD at femur neck and other variables rather the 4 mentioned above did not reach the statistical significance (table3).

Table 1. Baseline characteristics of 100 breast cancer patients

Variables		Value
Age (years), mean± SD		52.3 ± 8.2
Sex		
	Males n(%)	1 (1.0)
	Females n(%)	99 (99.0)
BMI (kg/m^2), mean± SD		30.3 ± 3.7
Time since breast cancer diagnosis(months) mean± SD		24.9 ± 22.6
Tumor stage		
	1	8 (8.0)
	2	28 (28.0)
	3	40 (40.0)
	4	24 (24.0)
Menarche age (years) mean± SD *		12.3 ± 1.5
Menopausal status *		
	Pre	38 (38.4)
	Post	61 (61.6)
Age at menopause (years) mean± SD *		47.7 ± 2.7
Years since menopause mean± SD *		9.3 ± 5.8
Parity *		
	Multi n (%)	83 (83.8)
	Nulli n (%)	16 (16.2)
Smoking history +ve n (%)		9 (9.0)
Treatment		
	Chemotherapy n (%)	100 (100.0)
	Radiotherapy n (%)	46 (46.0)
	Others n (%)	66 (66.0)
Joint mobility		
	Normal n (%)	78 (78.0)
	Increased n (%)	22 (22.0)
FRAX % score		
	Major osteoporotic # at any site mean ± $SE^{\$}$	8.3 ± 1.1
	Hip #	3.5 ± 0.9
ESR mm/h mean ± SD		46.9 ± 9.9
CRP no. of +ve		33 (33.0)

* females only , the % calculated with in females (n =99), SD: standard deviation of the mean; ESR, erythrocyte sedimentation rate; CRP, c-reactive protein;FRAX, fracture risk assessment

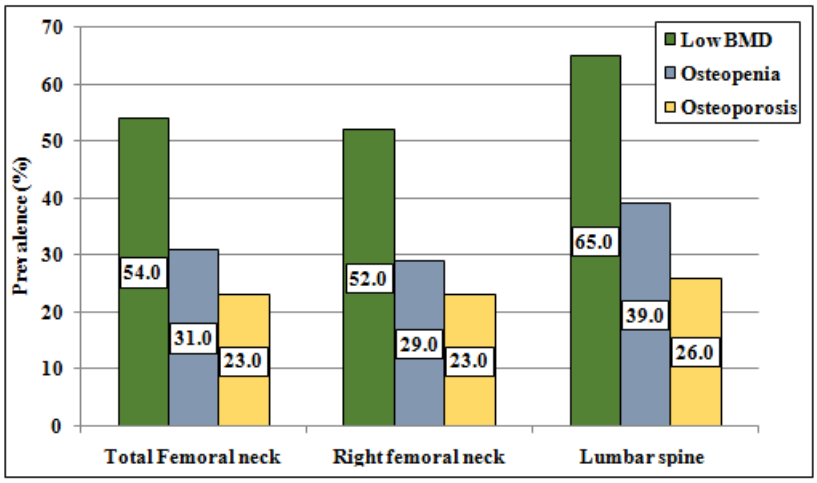

Figure 1. Prevalence of Low bone mineral density, Osteoporosis and Osteopenia at different sites

Table 2: Multiple logistic regression analysis for predictors of low BMD at spine

Variable	*B*	OR	P
Age (years)	**0.27**	**1.3**	**< 0.001**
BMI (kg/m^2),	.055	1.1	0.97
Time since breast cancer diagnosis	.067	1.07	0.052
Tumor stage	-1.063	0.35	0.17
Menarche age	0.06	1.1	0.60
Menopausal status	-0.34	0.71	0.47
Age at menopause	**-1.38**	**0.25**	**<0.001**
Years since menopause	-1.094	0.33	1.0
Parity	0.94	2.56	0.15
Smoking History (+ve)	0.104	1.11	0.92
Radiotherapy (+ve)	-0.65	0.52	0.17
Others (+ve)	0.15	1.16	0.82
Joint mobility	-0.08	0.92	0.82
FRAX %(score) for major osteoporotic # at any site	0.26	**1.30**	**0.006**
ESR (high)	-0.024	0.98	0.35
CRP (+ve)	**-1.98**	**0.14**	**0.001**

Sex and chemotherapy were not included in the model, only one male found, and for chemotherapy all patients received so and the correlation couldn't be applied

BMI, body mass index; OR: Odds ratio, B: beta; correlation coefficient; FRAX, fracture risk assessment; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein

Table 3: Multiple logistic regression analysis for predictors of low BMD at femur neck

	B	Odds ratio	P
Age (years)	**1.65**	**5.2**	**<0.001**
BMI (kg/m^2),	1.73	5.65	0.52
Time since breast cancer diagnosis	0.66	1.93	0.29
Tumor stage	-1.29	0.28	0.67
Menarche age	1.86	6.44	0.46
Menopausal status	-0.37	0.69	0.40
Age at menopause	**-1.06**	**0.35**	**<0.001**
Years since menopause	-0.25	0.78	1.00
Parity	-2.68	0.07	0.91
Smoking history (+ve)	-21.05	0.00	0.17
Radiotherapy (+ve)	0.41	1.51	0.95
Others (+ve)	2.73	15.37	0.25
Joint mobility	1.97	**7.20**	**0.014**
FRAX %score for # Hip	0.35	**1.41**	**0.005**
ESR mm/h (high)	-0.35	0.69	0.99
CRP (+ve)	-0.38	0.68	0.16

Sex and chemotherapy were not included in the model, all patients received chemotherapy, and only one male correlation couldn't be applied. BMI, body mass index; OR: Odds ratio, B: beta; correlation coefficient; FRAX, fracture risk assessment; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein

IV. Discussion

This study aimed to assess the prevalence and predictors of low BMD in Iraqi patients with BCA. To the best of our knowledge this is the first study to investigate BMD in Iraqi BCA patients.The present study showed a high frequency of osteopenia and osteoporosis in Iraqi patients with BCA. At the femoral neck, the prevalence of osteopenia was 29% and osteoporosis 23%. While at the lumbar spine 39% of the patients had osteopenia and 26% had osteoporosis.

In a study of postmenopausal BCA survivors, Twiss et al. [15]reported that 16.5% had osteopenia and 2.4% had osteoporosis according to total hip measurements. Another study [16] reported that a prevalence of osteopenia and osteoporosis was 25.7% and 2.8% at femoral neck, and 32.8% and 12.8% at lumbar spine respectively. These results are consistent with the present data with a higher prevalence of change at lumbar spine. Low BMD may be more prevalent at the lumbar spine because the trabecular bone which forms a major part of the vertebral body is highly responsive to hormonal alterations [17] common in the age group evaluated in the present study. The current data showed no significant association between low BMD and time since breast cancer diagnosis. Similarly, another study [18] consisting of 30 postmenopausal BCA survivors patients failed to show such association which is consistent with our findings. However another study of 70 BCA survivors patients showed an association between longer time since breast cancer diagnosis and a low BMD [17].Possibly due to different sample sizes.

In this study, age was a significant predictor for low BMD. Similar finding was reported by other authors [18,19] where age related bone loss has been found. However, other studies found no relationship between age & low BMD [20, 21].

Data also showed that women with advanced age at menopause were less likely to have low BMD at both spine & femur neck sites. This may due to the fact that estrogen has a protective effect on bones and plays a substantial role in maintaining bone health.A decrease in bone mass due to an imbalance between bone resorption and bone formation is typical of osteoporosis in women with estrogen depletion [22].

Patients with increased joint mobility scores were about seven folds more likely to have low BMD, this is in accordance with the findings of a previous study [23] which suggested that premenopausal women with joint hypermobility have lower bone density when compared to controls, and that hypermobility may increase the risk for low bone mass.

Another observation of note was that patients with high FRAX score for major osteoporotic fractures and hip fractures were more likely to have low BMD. This is clinically important because treatment of osteoporosis should be considered for patients with low bone mineral density and a ten-year risk of hip fracture of ≥3% or a ≥ 20% ten-year risk of a major osteoporosis-related fracture. The high low BMD of patients with BCA survivors may be related to clinical and geographical factors contained in FRAX assessment tool. [24].Data from this study showed that CRP was a significant predictor of low BMD at the lumbar spine but not at the femur neck site which could be attributed to the effect of other variables included in the multiple logistic regression model .Age of patient was significantly correlated with low BMD at both sites(spine & femur neck) but the correlation was stronger at the femur neck than at the spine (Odds ratio 1.3 & 5.2 , respectively), and the strong correlation of low BMD with joint mobility found at femur neck site rather than the spine , these two factors (the stronger correlation with age and strong correlation with joint mobility at femur neck site) might overcome the effect of CRP to be clear at femur neck site, particularly. This correlation was not strong enough to pass this competition where the Odds ratio at the spin site was (0.14).This finding was in agreement with other studies that found significant correlation between low lumbar spine BMD and elevated CRP [25, 26] indicating that controlling inflammation (elevated CRP) may improve low BMD.

The small sample size may be a limitation of current study. However this may be solved by a larger longer prospective study. In spite of that, the current study has strong points that include strict inclusion and exclusion criteria, and controlled the confounders by multiple logistic regression analysis.

In conclusion, Low BMD was common in Iraqi BCA patients. Older age females, high FRAX score, increased joint mobility score and increased levels of CRP were significant associates with low BMD. Advanced age at menopause was protective. Early screening of BCA patients for osteoporosis may prevent the risk of bone loss and life-threatening osteoporotic fractures.

Authors'contributions

All the authors involved in study design and conception, acquisition of data, and data analysis and interpretation.

References

[1]. Sariego J. Breast cancer in the young patient. The American Surgeon 2010; 76(12):1397-11401.
[2]. World Cancer Report. International Agency for Research on Cancer.2008.
[3]. Soules MR, Sherman S, Parrott E, et al. Executive summary:Stages of Reproductive Aging Workshop(STRAW) Park City, Utah, July, 2001. Menopause2001;8:402–7.
[4]. Prevention and management of osteoporosis. WHO Scientific Group. World Health Organization Technical Report Series 2003; 921:1-164
[5]. Gorial FI, Aubaese ND, Husaeen NH. Prevalence and associated factors of osteoporosis in postmenopausal Iraqi women:A Cross-Sectional Two Centers Study. I J Mod Bio and Med 2013; 3(1) :41-9
[6]. Vehmanen L, Saarto T, Elomaa I, et al. Long-termimpact of chemotherapy-induced ovarian failureon bone mineral density (BMD) in premenopausal breast cancer patients. The effect of adjuvantclodronatetreatment. Eur J Cancer 2001;37:2373–8.
[7]. Cameron DA, Douglas S, Brown JE, Anderson RA. Bone mineral density loss during adjuvant chemotherapyin pre-menopausal women with early breast cancer: Is it dependent on oestrogen deficiency?Breast Cancer Res Treat 2010;123:805–14.
[8]. Sowers MR, Zheng H, Jannausch ML, et al.Amount of bone loss in relation to time aroundthe final menstrual period and follicle-stimulating hormone staging of the transmenopause. J ClinEndocrinolMetab 2010;95:2155–62.
[9]. Waltman NL, Ott CD, Twiss JJ, et al. Bonemineral density and bone turnover in postmenopausalwomen treated for breast cancer. CancerNurs 2008;31:182–90.
[10]. Winters-Stone KM, Nail L, Bennett JA, SchwartzA.Bone health and falls: fracture risk in breastcancer survivors with chemotherapy-inducedamenorrhea. OncolNurs Forum 2009;36:315–25.
[11]. Ghimire B, Khan MI, Bibhusal T, et al. Accuracy of triple test score in the diagnosis of palpable breast lump. JNMA J Nepal Med Assoc. 2008;47(172):189-92
[12]. Beighton PH, Solomon L, Soskolne CL. Articular mobility in an African population. Ann Rheum Dis 1973;32:413-7.
[13]. Kanis JA, Johnell O, Oden A, et al. Ten year probabilities of osteoporotic fractures according to BMD and diagnostic thresholds. Osteoporos Int 2001, 12:989-995.
[14]. National Osteoporosis Foundation. (2008). Types of bone density tests. Retrieved September 4, 2008, from http://www. nof.org/osteoporosis/ bmdtest.htm# BMD_ Test_ Types. Accessed at 5/6/2014
[15]. Twiss JJ, Gross GJ, Waltman NL, et al. Health behaviors in breast cancer survivors experiencing bone loss. J Am Acad Nurse Pract 2006;18: 471–81.
[16]. Conde DM, Costa-Paiva L, Martinez EZ, Mendes Pinto-Neto A.Low Bone Mineral Density in Middle-Aged Breast Cancer Survivors: Prevalence and Associated Factors.Breast Care 2012;7:121–125
[17]. Chen Z, Maricic M, Bassford TL, et al.: Fracture risk among breast cancer survivors: results from the Women's Health Initiative Observational Study. Arch Intern Med 2005;165:552–8.
[18]. Zhai G, Hart DJ, Valdes AM, et al.: Natural history and risk factors for bone loss in postmenopausal Caucasian women: a 15-year follow-up population based study. Osteoporos Int 2008;19:1211–7
[19]. Nahas EA, Kawakami MS, Nahas-Neto J, et al. Assessment of risk factors for low bone mineral density in Brazilian postmenopausal women. Climacteric 2011;14::220–7.
[20]. Twiss JJ, Waltman N, Ott CD, et al.: Bone mineral density in postmenopausal breast cancer survivors. J Am Acad Nurse Pract 2001;13:276–84
[21]. Waltman NL, Ott CD, Twiss JJ, et al.: Bone mineral density and bone turnover in postmenopausal women treated for breast cancer. Cancer Nurs 2008;31:182–90.
[22]. Imai Y, Kondoh S, Kouzmenko A, Kato S: Mini-review: osteoprotective action of estrogens is mediated by osteoclastic estrogen receptor-alpha. Mol Endocrinol 2010;24:877–85
[23]. Gulbahar S, Sahin E, Baydar M, et al. Hypermobility syndrome increases the risk for low bone mass. Clin Rheumatol. 2006;25 (4):511-4.
[24]. Unnanuntana A, Gladnick BP, Donnelly E, and Lane JM. The Assessment of Fracture Risk.J Bone Joint Surg Am. Mar 2010; 92(3): 743–53.
[25]. Jun JB, Joo KB, Her MY, et al. Femoral bone mineral density is associated with vertebral fractures in patients with ankylosing spondylitis: a cross-sectional study. J Rheumatol 2006, 33:1637-1641.
[26]. Klingberg E, Lorentzon M, Mellström D, et al.Osteoporosis in ankylosing spondylitis - prevalence, risk factors and methods of assessment.Arthritis Res Ther. 2012; May 8;14(3):R108.