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Post-menopausal breast cancer risk and vitamin D in Al-imamain Al-kadhumain Medical City in Baghdad: A cross-sectional Study

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بِسمِ اللهِ الرَّحمنِ الرَّحيم

الَّذِي خَلَقَنِي فَهُوَ يَهْدِينِ (78) وَالَّذِي هُوَ يُطْعِمُنِي وَيَسْقِينِ (79) وَإِذَا مَرِضْتُ فَهُوَ يَشْفِينِ(80)

صدقَ اللهُ العظيم

سورة الشعراء

Dedication

To our wounded and patient country "Iraq".

To our families for their abundant support.

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First of all, we would like to praise Allah the Almighty, for helping me complete this work.
I am extremely grateful to our supervisor "Dr. kahtan for giving me the opportunity to work under his supervision. I would like to thank him for the endless support, encouragement, and guidance; it was a pleasure working with him.
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Objectives of the study

To assess the relation of vitamin D with Post-menopausal breast cancer risk.

Abstract

Introduction:

Breast cancer survivors (BCS) taking aromatase inhibitors (AIs) are at an increased risk for decreased bone density and fractures. Given the role vitamin D plays in bone metabolism, we examined the prevalence of and risk factors for vitamin D deficiency in a study of postmenopausal BCS on AIs.

Materials and Methods:

We collected data on 20 postmenopausal women with stage I–III breast cancer on AI therapy. Vitamin D levels were measured by radioimmunoassay from patients' sera in outpatient ; deficiency was defined as a level < 30 ng/mL. Multivariate models were created to assess risk factors for deficiency. Descriptive and analytical statistics were performed using the by SPSS version 23.0.

Results:

The median vitamin D level was 25 ng/mL (range 6.78–93.15), and 35% of women were vitamin D deficient. When adjusting for age and vitamin D supplementation. Both overweight (AOR 3.05, 95% CI 1.72-5.41, $p<0.001$) and obese participants (AOR 3.21, 95% CI 1.79-5.78, $p<0.001$) had higher deficiency rates than did normal weight participants.

Conclusion:

Hypovitaminosis D is common in BCS, and those who are overweight are at a higher risk of deficiency despite taking vitamin D supplements.

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AIs	Aromatase Inhibitors
BMI	Body mass index
BCS	Breast cancer survivors
VDR	Vitamin D receptors

Chapter One

Introduction

Breast cancer was estimated one of the most commonly diagnosed cancer worldwide (11.9**%**) [(1)].Among women, it is the most common cause of cancer death and the most frequently diagnosed cancer in 140 out of 184 countries worldwide [(2)]. The incidence is decreasing every year, which is partly due to early detection programs [(3)].

Many factors have been claimed to increase breast cancer risk, from which are; weight gain and body mass index; age at menarche and menopause, previous benign breast lesions, family history of breast cancer, exposure to ionizing radiation and alcohol consumption[(4)].

Vitamin D (vit D) through its binding to vitamin D receptors (VDR) which are located in the nuclei of the breast cells among other tissues of the body exerts variety of immunological and anti-proliferative activities [(5)]. That is why suboptimal Vit D levels might lead to cancer development through impairment of cell proliferation, differentiation, apoptosis and angiogenesis.

Interestingly, it has been found that people with high sun exposure, higher intake or higher serum levels of Vit. D showed reduced incidence of breast, colon, and prostate cancers [(6)].

In the liver, Vit D is metabolized to 25-hydroxy vitamin D, and then further hydroxylated by 1-alpha hydroxylase enzyme in kidneys and other tissues like breast, prostate and colon cells to 1-25dihydroxy vitamin D, the most biologically active form and the natural ligand for VDR [(7)].

Circulating 25 (OH) D concentrations is considered the best indicator of vitamin D status and the major storage form and varies with dietary intake and exposure to sunlight [(2&8)]. On the other hand, the circulating concentration of 1, 25(OH) D is

tightly regulated by renal 1-alpha –hydroxylase, so its level is maintained in a relatively low rang [9].

Vitamin D deficiency is also associated with secondary elevation in PTH serum levels which has carcinogenic and tumor promoting effects hence, may lead to an increase risk of breast cancer [10].

In the last decades, cellular in vitro experiments and in vivo models have evaluated the role of vitamin D in the development of breast cancer, finding a protective anticancer role of 1,25(OH)D3[3]. It has been demonstrated that treating breast cancer cells with 1,25(OH)D3 induces two beneficial effects: an anti-proliferative effect4 and a pro-apoptotic effect [5,6]. The former is linked to the suppression of growth stimulatory signals and the potentiation of growth inhibitory signals, whilst the second one is explained by the bcl-2 family proteins. The interaction between vitamin D and its receptors induces an increase in the expression of pro-apoptotic family member (bax and bak protein) and simultaneously a decrease of anti-apoptotic (bcl-2/bcl-XL) [6]. In addition, the breast tissue contains the 1-α-hydroxylase, allowing for the generation of the active vitamin D metabolite (1,25 dihydroxyvitamin D) from the circulating precursor (25 hydroxyvitamin D). As vitamin D receptors are found in the breast [11], an autocrine role of vitamin D has been suggested.

Aim of the work is to evaluate the association between abnormal serum levels of 25 (OH) D in postmenopausal female patients with breast cancer.

Chapter Two
Methods & Materials

2.1 Study setting

We conducted a cross-sectional study of women taking Aromatase Inhibitors (AIs) in Al-imamain Al-kadhumain Medical City in Baghdad. Twenty postmenopausal women with breast cancer were selected. Potential study participants included postmenopausal women with a history of histologically confirmed, stage I–III, hormone receptor-positive breast cancer who were currently taking a third-generation AIs (anastrozole, letrozole, or exmestane) and visited the hospital between March 2019 and April 2019. Additional inclusion criteria were completion of chemotherapy or radiotherapy at least 1 month before enrollment in the study, and the patient's ability to understand and provide informed consent. After informed consent was obtained, each participant completed a self-administered survey.

2-2. Demographic and clinical Information

Patients completed a survey that queried demographic and medical variables, including age, body mass index (BMI), education level, employment status, and such medical comorbidities as osteopenia and osteoporosis. Chart abstraction was performed for data about such variables as breast cancer stage, chemotherapy, vitamin D supplementation, and previously documented serum vitamin D levels.

2-3. Statistical analysis

After collecting the necessary information, data entered in SPSS version 23.0. To describe the data of central tendency and dispersion, mean and standard deviation (SD) were used. Descriptive analyses for demographics, clinical characteristics, and serum vitamin D levels were performed. We used chi-square analyses to assess the differences between patients who were found to be vitamin

D deficient vs. those who were vitamin D sufficient. The level of significance less than 0.05 considered statistically significant.

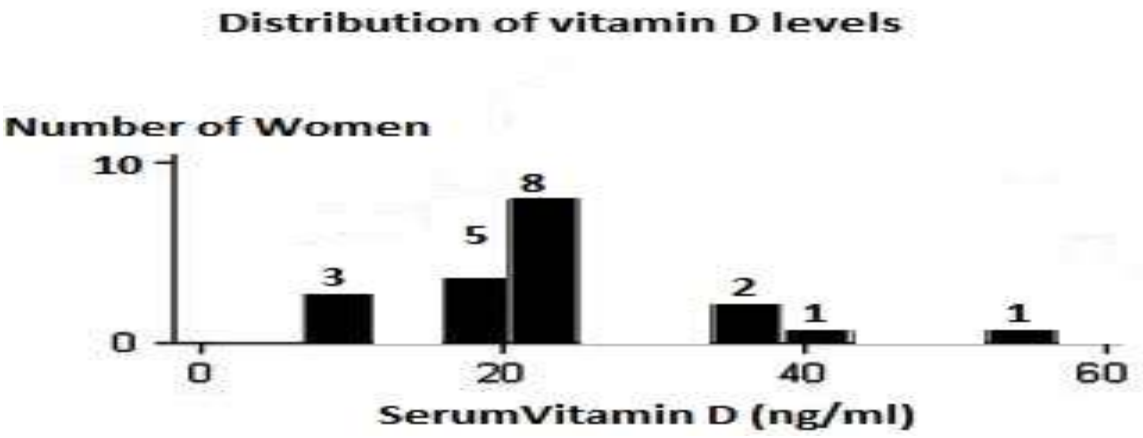
Chapter Three Results

Among the 20 study participants, the mean age was 61 years, ranging from 33 to 81 years. **Table 1** includes further demographic and clinical information.

Table 1. Vitamin D Status and Clinical Characteristics (*n*=20)				
	Total number of participants	Vitamin D replete	Vitamin D deficient	p value
Age				0.841
<55	24% (4)	68.1% (3)	31.9% (1)	
55–65	45% (10)	65% (7)	35% (3)	
>65	31% (6)	66.5% (4)	33.5% (2)	
BMI				
<25	41% (11)	80.8% (8)	19.3% (3)	**<0.001**
25–30	31% (5)	57.4% (3)	42.6% (2)	
>30	28% (4)	55.6% (3)	44.4% (1)	
Education level				
High school or less	19% (4)	59.2% (3)	40.8% (1)	0.311
College	45% (10)	67.2% (7)	32.8% (3)	
Graduate or professional	36% (6)	69.3% (4)	30.7% (2)	
Employment				
Full-time	41% (5)	60.8% (3)	39.2% (2)	
Part-time	13% (3)	78% (2)	22% (1)	0.067
Not currently employed	46% (12)	67.8% (9)	32.2% (3)	
Cancer stage				
Stage I/0	39% (6)	70.9% (4)	29.1% (2)	0.262
Stage II	48% (11)	64.9% (8)	35.1% (3)	
Stage III	13% (3)	59.2% (2)	40.8% (1)	
Chemotherapy				
No chemotherapy	39% (15)	71.1% (11)	29% (4)	0.105
Chemotherapy	23% (5)	57.8% (3)	52.2% (2)	
Vitamin D supplementation				**p<0.001**
No	27% (4)	48.1% (1)	51.9% (3)	
Yes	73% (16)	72.2% (13)	26.8% (3)	
Bone health				
Neither	54% (14)	60.2% (10)	39.8% (4)	**0.014**
Osteopenia	31% (3)	75.4% (2)	24.6% (1)	
Osteoporosis	15% (3)	70.7% (2)	29.3% (1)	

Vitamin D distribution

The mean vitamin D level was 25 ng/mL, standard deviation (SD) 10 ng/mL. Vitamin D levels were normally distributed in our population **(Fig. 1)**. Using the aforementioned definitions of vitamin D deficiency, we found that 35% of patients were vitamin D deficient.



(Figure 1): Vitamin D distribution

Risk factors for vitamin D deficiency

In bivariate analysis (Table 1), BMI, part-time employment, and vitamin D supplementation were all significantly associated with vitamin D deficiency.

In the multivariate model incorporating clinical and demographic factors **(Table 2)**, BCS who were overweight (adjusted odds ratio [AOR] 3.07, 95% confidence interval [CI] 1.77- 5.33, $p<0.001$) or obese (AOR 2.88, 95% CI 1.64-5.06, $p<0.001$) had a significantly higher risk of being vitamin D deficient. Employment became nonsignificant in this model.

Table 2.Multivariate Model of Vitamin D Status (Deficient Yes/No) Versus Clinical and Demographic Factors.					
Characteristic		*Bivariate analysis*		Multivariate model[a]	
		OR (95% CI)	p	AOR (95% CI)	p
Age, years	<55 9(reference)				
	55-65	1.15(0.68-1.96)	0.607	0.98 (0.54-1.77)	0.949
	>65	1.03(0.58-1.83)	0.928	1.16 (0.55-2.43)	0.694
BMI	<25 (reference)				
	25-30	3.12(1.83-5.30)	<0.001	3.05 (1.72-5.41)	**<0.001**
	<30	3.35(1.94-5.79)	<0.001	3.21 (1.79-5.78)	**<0.001**
Employment	Full-time (reference)				
	Part-time	0.44(0.21-0.92)	0.029	0.40(0.18-.92)	**0.03**
	Noemployed	0.74(0.47-1.15)	0.179	0.66 (0.37-1.17)	0.152
Vitamin D supplementation	No (reference)				
	yes	0.34(0.21-0.54)	<0.001	0.29 (0.17-0.48)	**<0.001**
Model [a] : additionally adjusts for vitamin D supplementation. AOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio.					

Impact of vitamin D supplementation on vitamin D deficiency

In our study, 73.4% had vitamin D supplementation documented in their charts. They were significantly less likely to be vitamin D deficient compared to those women not on vitamin D supplementation (26.8% vs. 51.9%, p<0.001). To further elaborate this finding, we created a second multivariate model that incorporated vitamin D supplementation into the previous multivariate model **(Table 2)**. As expected, vitamin D supplementation was associated with a lower risk of vitamin D deficiency (AOR 0.29, 95% CI 0.17-0.48, p<0.001). Interestingly, the risk for BCS who were overweight (AOR 3.05, 95% CI 1.72- 5.41, p<0.001) or obese (AOR 3.21, 95% CI 1.79-5.78, p<0.001) increased when adjusting for vitamin D supplementation.

Chapter Four

Discussion

In this study among a cross-sectional of postmenopausal BCS on AI, we found that 35% of women were vitamin D deficient, and of those, 58.8% were already receiving supplementation. Women who had a BMI > 25 regardless of race were more likely to be vitamin D deficient. In our study, despite the fact that one third of BCS have vitamin D deficiency, only 43% of our study had a vitamin D level documented in their chart. Women with osteoporosis were less likely to be vitamin D deficient and more likely to have vitamin D levels ordered and documented in their chart by their oncologist compared to other BCS.

Our findings are consistent with numerous studies that have demonstrated that the vitamin D deficiency rate among breast cancer patients is >30% **[19,21]**. A recent study by Crew et al.[20] found a deficiency rate of 74% among breast cancer patients on chemotherapy. The difference in deficiency rates may be due to the difference in racial composition of the two studies. The difference may also be explained by differing rates of vitamin D supplementation between the two studies or differences in diet or UV exposure.

Surprisingly, 26.8% of the women currently receiving vitamin D supplementation were vitamin D deficient. This finding raises the possibility that some levels of supplementation may not be adequate. A previous study found that after supplementation with 400 IU daily for 1 year, <15% of white and Hispanic women and no black women achieved sufficient vitamin D levels.20 The current Institute of Medicine (IOM) recommended daily allowance (RDA) for vitamin D is 600 IU for women aged 51–70 and 800 IU for women aged ≥70.24 Although we were unable to determine from the chart the exact number of international units of vitamin D that each participant was taking, these data suggest that the amount being taken may not be sufficient for some individuals to correct vitamin D deficiency in this study of women.

The 2005 Dietary Guidelines for Americans recommends that groups at high risk for vitamin D deficiency, including older adults, people with dark skin, and those exposed to insufficient UV radiation, should consume 1000 IU vitamin D daily[19]. One study found that postmenopausal African American women required 2000 IU daily to achieve a sufficient serum vitamin D level, highlighting that for vitamin D supplementation, one size may not fit all[20]. Given the uncertainty surrounding the

appropriate vitamin D supplementation dosage for minority patients, it is not surprising that a large percentage of them remain vitamin D deficient.

Obesity is another well-documented risk factor for vitamin D deficiency. Numerous studies have demonstrated a relationship between obesity and serum vitamin D levels, irrespective of race[8,11–13]. This is consistent with our findings, in which both overweight (BMI 25–30) and obese (BMI >30) women were about three times as likely to be vitamin D deficient as those BCS with a BMI ≤ 25. In addition, we found that controlling for vitamin D supplementation in our multivariate model increased the AOR of vitamin D deficiency for overweight and obese women, suggesting that women with a BMI <25 are more easily able to achieve sufficient levels with recommended levels of supplementation. The exact mechanism for this phenomenon is still unknown. One theory is based on the fact that vitamin D is lipophilic, leading to increased fat uptake of vitamin D among more obese women. Mower et al. found that radiolabeled cholecalciferol injected intravenously into adipose tissue was rapidly cleared, suggesting that vitamin D is sequestered in adipose tissue in overweight and obese individuals and, thereby, not bioavailable[14,15]. Other researchers theorize that overweight women may feel more self-conscious about exposing their skin, thereby decreasing their UV exposure and endogenous production of vitamin D. It is also possible that increased weight may merely be the result of a nutritionally poor diet that is low in sources of vitamin D. These interesting hypotheses need to be explored in future research.

Although overweight and obese patients are at a lower risk for decreased bone density, obesity is a negative prognosis factor for several events related to breast cancer, including overall survival [16]. It is unclear if vitamin D deficiency plays a causal role for these increased risks, but correcting a vitamin D deficiency may have the potential to improve outcomes for these BCS. This requires greater awareness on the part of physicians to diagnose and treat vitamin D deficiency in overweight or obese women, but we found no increase in vitamin D level documentation or supplementation in this subpopulation of our study. This clinical scenario is complicated by the fact that patients with increased BMI may require increased supplementation compared to BCS of normal weight[17]. Unfortunately, there is uncertainty about what constitutes adequate supplementation for overweight or obese patients.

Although we found that patients with self-reported osteopenia or osteoporosis had lower rates of vitamin D deficiency compared to their counterparts, the deficiency rates were still quite high, 22% and 29.2%, respectively. Vitamin D status is a special concern for BCS on AIs because of its well-established relationship to bone mineral density (BMD) [7,21]. Women on AIs are at an increased risk of decreased BMD and fracture. One study of a cohort of BCS found that after 5 years of anastrozole, there was a 6.08% decrease in median BMD in the lumbar spine and a 7.24% drop in the total hip[18]. BCS on AIs also have an AOR of 2.03 for any type of fracture compared to nonusers[19]. Given evidence that vitamin D may prevent osteoporotic fractures[10,11], it may be important to understand how much vitamin D supplementation may help prevent osteoporosis and fracture in this population.

Chapter five

Conclusion
References

CONCLUSION

Despite the growing body of literature that suggests the importance of vitamin D for BCS, vitamin D deficiency rates remain relatively high in this population. Although the efficacy of vitamin D supplementation for reducing breast cancer mortality is still uncertain, there is a known benefit of vitamin D for maintaining BMD and decreasing the osteoporotic fracture rate[20,21]. Given the documented risk of fractures associated with AI therapy [6], this is a particularly relevant clinical problem. Practitioners should be aware that overweight or obese women and ethnic minorities are at the highest risk for being vitamin D deficient. In addition, the amount of vitamin D supplementation recommended by IOM guidelines may not be enough to raise vitamin D levels to an appropriate level, especially in these high-risk groups. More research is needed to establish vitamin D supplementation guidelines for nonwhite and overweight patients. Clinicians should be aware that a one size fits all approach to supplementation may not be adequate.

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