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A Longitudinal Study for the Effect of Vitamin D Adjunct to Chemotherapy on Non-Metastatic Breast Cancer Patients after Mastectomy

Ehab I. Mohamed[1*], Azza M. Helal[2,3], Noha M. Awad[4], Gihane I. Khalil[5], Amani M. Bayoumi[6] and Nadia A. Abd El Moneim[7]

*Correspondence: eimohamed@yahoo.com ; ehab.abdo@alexu.edu.eg

[1]Medical Biophysics Department, Medical Research Institute, Alexandria University, Alexandria, Egypt.
[2]Physics Department, King Abdulaziz University, Jeddah, Saudi Arabia.
[3]Medical Physics Unit, Radiology and Intervention Department, Faculty of Medicine, Alexandria University, Alexandria, Egypt.
[4]Epidemiology Department, High Institute of Public Health, Alexandria University, Alexandria, Egypt.
[5]Chemical Pathology Department, Medical Research Institute, Alexandria University, Alexandria, Egypt.
[6]Physics Department, Faculty of Science, Alexandria University, Alexandria, Egypt.
[7]Cancer Management and Research Department, Medical Research Institute, Alexandria University, Alexandria, Egypt.

Abstract

Background: Women with BC are at increased risk for the development of osteoporosis and skeletal fractures. We investigated the effect of CAF chemotherapy alone and adjunct to vitamin D treatment on biochemical markers of bone formation and on segmental and total bone mineral density (BMD) for non-metastatic breast cancer (NMBC) postmenopausal women who had gone through a mastectomy.

Methods: The study population was comprised of 200 NMBC women who were divided into two equal groups; before and after treatment with CAF chemotherapy alone and before and after treatment with CAF+Vitamin D treatment protocols. Other 100 healthy participants served as the Control group. All participant women were subjected to blood biochemical analysis and segmental and total BMD measurements using Dual-energy X-ray Absorptiometry technique.

Results: We found that CAF chemotherapy alone had no effect on women's body weight, BMI, tumor marker CA15-3, PTH, ALP and Ca levels as compared to the initial state, while CAF+Vitamin D adjunct treatment caused significant reductions in their levels as compared to the initial state and Healthy Controls. We found also that CAF chemotherapy alone had no effect on plasma levels of P and Vitamin D as compared to initial state yet, CAF+Vitamin D adjunct treatment caused significant elevations in their levels as compared to the initial state and Healthy Controls.

Conclusions: Vitamin D may decrease the risk of BC recurrence by decreasing risk factors like body weight and serum levels of CA15-3, PTH, ALP, and Ca, thus increasing segmental and total BMD and decreasing the risk of osteoporosis.

Keywords: Vitamin D, Chemotherapy, Breast Cancer, Bone Mineral Density, Osteoporosis, Dual-energy X-ray Absorptiometry

Introduction

Breast cancer (BC) (i.e., invasive ductal carcinoma, invasive lobular carcinoma, Paget's disease, medullary, mucinous, and inflammatory BC) is the most common invasive cancer and the second most common cause of cancer death, after lung cancer, in women worldwide [1,2]. Its estimates amounted a total of 2.1 million each year, causing 627,000 deaths that are approximately 15% of all cancer deaths among women in 2018 [2,3]. According to the National Population-Based Registry Program, BC was the most prevalent cancer among Egyptian women in the period 2008-2011, representing 15.41% of total cancer cases with an age-standardized rate of 24.3/100,000

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individuals (32.04% and 48.8/100,000 for women and 0.51% and 0.9/100,000 for men; respectively) [4,5].

Prognosis and survival rate of BC patients have been improved considerably, making BC curable cancer, yet with long-term complications in bone health resulting from the treatment given or cancer itself [6]. In fact, chemotherapy-induced menopause, aromatase inhibitors, radiation therapy, and long-term bisphosphonate consumption can all increase bone resorption without a corresponding increase in bone formation [7], resulting in loss of bone mineral density (BMD) [8]. Compared to healthy postmenopausal women who may lose ~1% of their BMD per year, women with BC lose 2-3 fold more BMD, increasing the risk of hip and vertebral fractures, which are associated with a significant decline in function, quality of life, and higher mortality rates [9]. Recently, there has been considerable interest in the potential effects of serum vitamin D [25-hydroxyvitamin D; 25(OH)D] concentrations in the etiology of BC [10]. Besides the essential role of vitamin D in calcium homeostasis and bone metabolism, vitamin D can induce cell differentiation, inhibit cell growth and regulate apoptosis in normal and malignant cells, including human BC cells [11,12].

The objectives of this study were to investigate the effect of chemotherapy for a period of 6 cycles adjunct to vitamin D treatment on biochemical markers of bone formation and on segmental and total BMD for non-metastatic breast cancer (NMBC) postmenopausal women who had gone through a mastectomy.

Patients and methods

Patients

The study population was comprised of 300 women and were divided into three groups: women with NMBC (*n*=100) before and after receiving 6-cycles of a three-drug Cyclophosphamide, Adriamycin, and 5-Fluorouracil (CAF) chemotherapy alone. Women with NMBC (*n*=100) before and after receiving CAF + Vitamin D treatment protocol. Other 100 apparently healthy women matching for age, weight and socioeconomic level of patient relatives served as the Healthy Control group. Participants were recruited from among patients referred to the Department of Cancer Management and Research, Medical Research Institute, Alexandria University; for diagnosis, treatment, and follow-up. All participants were asked to freely volunteer to the study protocol and to provide a signed informed consent prior to their inclusion in the study. The study protocol was approved by the Ethical Committee of the Medical Research Institute, Alexandria University, Alexandria, Egypt.

Women with NMBC (stage I–III) were diagnosed according to TNM classification [13] after surgery; were investigated before and after vitamin D intramuscular injection of vitamin D (Devarol-S-200.000 I.U. Amp. Memphis for pharmaceuticals & Chemical Industries) once per month adjunct to chemotherapy for a period of 4 months.

Methods

All women were subjected to complete history taking and history of previous bone fractures. Age of menopause was determined by self-report. And also the following analyses were performed to all participants using standard methods:

Blood Biochemical Analyses

Fasting blood samples were collected from all participant women to determine serum levels of CA15-3 by chemiluminescence technique (Immulite 1000, Siemens Healthcare Diagnostics Inc., Flanders, NJ, USA) [14]; Calcium (Ca) using a semi-automatic chemical analyzer (Olympus AU 400, Olympus Life and Material Science, Europe GmbH, Hamburg, Germany) [15]; Phosphorus (P), Alkaline Phosphatase (ALP) and Parathyroid hormone (PTH) [16]; and Vitamin D [25(OH)D] [17].

Imaging, Body-Composition and Bone Densitometric Measurements

Imaging studies were carried out for all participant women using Chest X-ray, abdominal and pelvic ultrasound and mammography. Demographic and body-composition variables were also measured for all participant women. Specifically, body weight (*kg*) (participants clothed in underwear, bare feet) was measured using a digital scale sensitive to the nearest 0.01 kg (Electronic Body Scale, TCS–200–RT, China). Height (*m*) was measured using a stadiometer. BMI was calculated as Weight/Height^2 (kg/m^2). Segmental (i.e., head, arms, trunk, ribs, spine, pelvis and legs) and total bone mineral content (BMC) and BMD were assessed using a Dual-energy X-ray Absorptiometry (DXA) total body scanner (Lunar DXP Pro, GE Health Care, USA), as detailed earlier by our group [18,19].

Statistical analysis

Data were fed to the computer and analyzed using SPSS software package version 20.0 [20]. Qualitative data were described using the number and percent. Quantitative data were described using Range (minimum and maximum), mean, standard deviation (SD) and median. The distributions of quantitative variables were tested for normality using Kolmogorov-Smirnov test, Shapiro-Wilk test, and D'Agstino test if it reveals normal data distribution, parametric tests were applied. If the data were abnormally distributed, non-parametric tests were used. For normally distributed data, a comparison between the three studied groups were analyzed using *F*-test (ANOVA) and post-*hoc* test (Scheffe) for pair-wise comparisons, also paired *t*-test was used to analyze two paired data. Significance of the obtained results was judged at the 5% level.

Results

The study population was comprised of 300 women, who were divided into three groups: women with NMBC (stage I–III) diagnosed according to TNM classification, before (*n*=100) and after (*n*=97) receiving 6-cycles of CAF chemotherapy alone, with a mean age (±SD) of 50.08±11.26 and range 29.60-71.20 year. Women with NMBC before (*n*=100) and after (*n*=99) receiving CAF + Vitamin D treatment protocol, with a mean age

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50.93±10.77 and range 32.80-64.80 year. Other 100 apparently healthy women matching for age, weight and socioeconomic level of patient relatives served as the Healthy Control group, with a mean age 48.75±7.71 and range 39.10-63.50 year. Demographic characteristics and biochemical parametersfor all study participants are shown in **Table 1**.

CAF chemotherapy alone had no effect on post-treatment women's body weight, BMI, tumor marker CA15-3, PTH, ALP and Ca levels as compared to pre-treatment state, while CAF + Vitamin D adjunct treatment caused significant ($p<0.05$) reductions in their post-treatment levels as compared to pre-treatment state and Healthy Control group. In the same way, CAF chemotherapy alone had no effect on post-treatment plasma levels of P and vitamin D as compared to pre-treatment state yet, CAF + Vitamin D adjunct treatment caused significant ($p< 0.05$) elevations in their post-treatment levels as compared to pre-treatment state and Healthy Control group, **Table 1**.

CAF chemotherapy alone reduced significantly ($p<0.001$) segmental (i.e., head, arms, trunk, ribs, spine, pelvis, and legs) and total BMD as compared to pre-treatment state and Healthy Control group, as shown in **Figure 1**. However, CAF + Vitamin D adjunct treatment was responsible for a significant ($p<0.01$) post-treatment increase in segmental and total BMD as compared to pre-treatment state.

Discussion

BC is the most common cancer, yet albeit the huge progress achieved in its treatment during past decades, it is still the principal cause of cancer death among the female population worldwide [1,2]. Vitamin D is one of the critical factors for female reproductive health, which may have protective effects against many cancer types, including BC [**21**,**22**]. This vitamin is a secosteroid hormone, which regulates the expression of a large number of genes important for female reproduction and health [**21**]. Low serum levels of vitamin D were found to be common at BC diagnosis with a poor prognosis in terms of overall survival and distant disease-free survival, particularly in postmenopausal females [**22**]. Vitamin D inhibits the growth of tumor-derived cells from breast, promotes apoptosis in BC cells, and acts as a cancer inhibitor (e.g., enhanced DNA repair, immunomodulation, and protection against antioxidants) [**11**,**12**]. However, there is a breakdown of vitamin D in tumor cells, causing resistance to the antitumor effects of vitamin D [**22**]. We found the majority of participant BC women in this study to have vitamin D levels as low as <32 *ng/ml*, prior to initiating CAF chemotherapy, findings which are similar to recent pooled analysis of three trials showing that BC risk is markedly higher with serum vitamin D concentrations <20 *ng/ml* [**10**].

Body weight and BMI of BC patients did not differ with CAF chemotherapy after mastectomy, while CAF + Vitamin D adjunct treatment caused a significant ($p<0.001$) reduction in their levels, as compared to the initial state and Healthy Controls, **Table 1**. The main effect of the active vitamin D metabolite $1,25(OH)_2D$ is to tonic the body making it tighter and to stimulate the absorption of Ca from the gut increasing BMD significantly [**23**]. In line with this, individual segmental and total BMD data showed significant elevations after CAF + Vitamin D adjunct treatment making their values comparable to Healthy Controls, **Figure 1**.

Our results showed that CA15-3 levels did not differ after CAF chemotherapy, yet decreased significantly ($p<0.001$) with CAF+ Vitamin D adjunct supplementation. Patients with high levels of CA15-3 have a significantly worse prognosis with BC recurrence than those with low levels [**24**]. It showed also that PTH levels increased significantly ($p<0.001$) after chemotherapy, but decreased significantly ($p<0.001$) with CAF+Vitamin D adjunct supplementation treatment, thus increasing BC

Table 1. Demographic characteristics and blood biochemical parameters assayed for non-metastatic breast cancer (NMBC) women before and after receiving 6-cycles of a three-drug Cyclophosphamide, Adriamycin, and 5-Fluorouracil (CAF) chemotherapy alone; before and after receiving CAF + Vitamin D treatment protocol; and Healthy Control women.

	CAF Alone		CAF + Vitamin D		Healthy Control
	Before (*n=100*)	***After*** (*n=97*)	***Before*** (*n=100*)	***After*** (*n=99*)	(***n*=100**)
Age (year)	50.08±11.26	50.72 ± 11.92	50.93 ± 10.77	51.54 ± 11.41	48.75 ± 7.71
Height (m)	1.57 ± 0.05	1.58 ± 0.05	1.54 ± 0.06	1.55 ± 0.06	1.61 ± 0.06
Weight (kg)	83.15 ± 9.37	85.12 ± 8.62	81.79 ± 8.79	72.54 ± 9.20*	83.11 ± 7.08
Body Mass Index (BMI, kg/m^2)	33.25 ± 2.40	34.90 ± 2.13	34.98 ± 2.88	30.31 ± 2.74*	32.06 ± 2.95
Tumor Marker CA15-3 (CA15-3, U/ml)	45.65 ± 7.71	46.25 ± 8.03	44.10 ± 8.61	31.24 ± 7.92*	19.38 ± 8.50
Parathyroid Hormone (PTH, pg/ml)	61.27 ± 7.39	84.37 ± 8.97*	65.96 ± 8.98	54.82 ± 8.50*	61.67 ± 7.31
Alkaline Phosphatase (ALP, U/l)	87.65 ± 14.05	95.42 ± 14.38	86.65 ± 9.53	61.75 ± 9.38*	68.45 ± 7.35
Calcium (Ca, mg/dl)	9.14 ± 0.32	9.01 ± 0.38	9.36 ± 0.34	8.57 ± 0.39*	9.36 ± 0.37
Phosphorus (P, mg/dl)	3.75 ± 0.55	3.89 ± 0.46	3.98 ± 0.56	4.56 ± 0.55*	3.50 ± 0.57
Vitamin D[25(OH)D, ng/dl]	9.69 ± 2.05	9.73 ± 2.80	9.65 ± 2.95	49.14 ± 2.25*	13.08 ± 2.36

Values are expressed as mean ± SD.
Statistical analysis using Paired *t*-test for comparing between Before and After and *post-hoc* test (Scheffe) of ANOVA versus Healthy Control women at *$p<0.05$.

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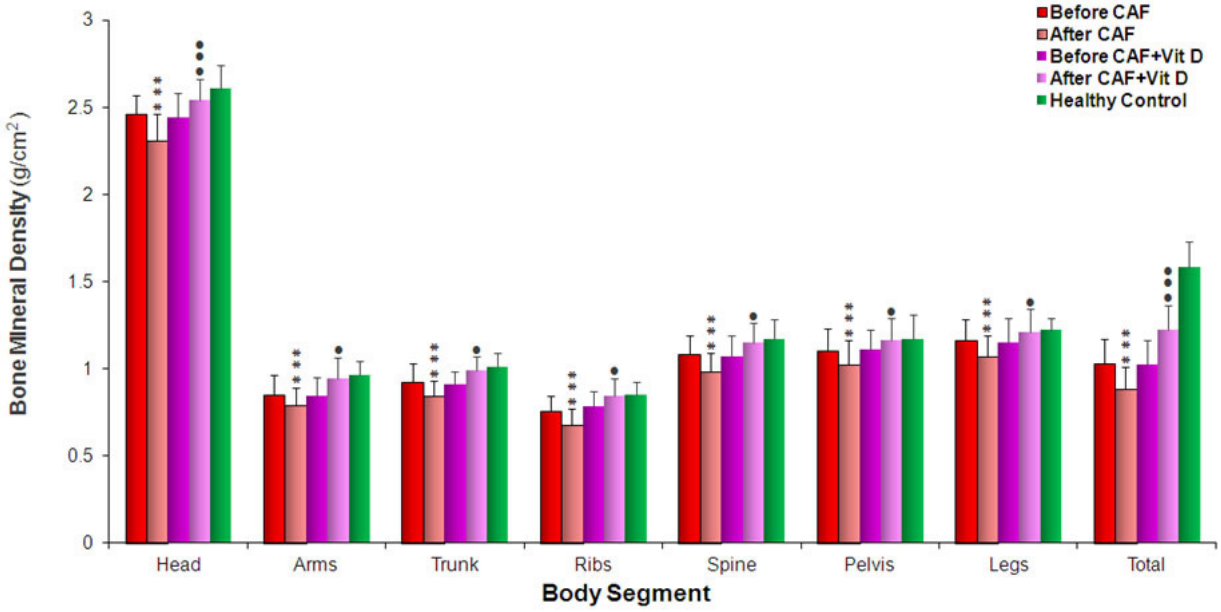

Figure 1. Bar-plot of segmental and total Bone Mineral Density (BMD, g/cm^2) measured using the Dual-energy X-ray Absroptiometry (DXA) technique for Healthy Control women (n=100), Non-Metastatic Breast Cancer women before (n=100) and after (n=97) receiving 6-cycles of a three-drug Cyclophosphamide, Adriamycin, and 5-Fluoruoracil (CAF) chemotherapy alone and before (n=100) and after (n=99) receiving CAF + Vitamin D treatment protocols. *p<0.05 versus Before CAF, **p< 0.01 versus After CAF+Vit D and Healthy Control and• ••p< 0.01 versus Before CAF+Vitamin D and Healthy Control, respectively.

survival. It had been suggested that PTH may be associated with a high risk of BC due to carcinogenic and tumor-promoting effects [25]; such as regulating angiogenesis and osteoclastogenesis in bone metastasis by BC cells [26].

ALP increased significantly (p<0.05) after CAF chemotherapy, but when adjunct to vitamin D treatment, it caused a significant reduction in its levels, which is considered a healthy sign, since ALP is a bone turnover marker. Elevated serum ALP level is considered an essential marker for the diagnosis of vitamin D deficiency, where vitamin D deficiency was diagnosed accidentally on the basis of elevated ALP levels [27]. More to add, physicians, have long recognized that elevated ALP in cancer patients usually signifies that the disease has spread to their bones. However, primary cancers in various organs can generate ALP elevations in the absence of metastasis [28]. CA15-3 was a better predictor of BC recurrence than ALP alone, but the use of both biomarkers together provided a better early indicator of recurrence. Elevated BC tumor marker CA15-3, in conjunction with ALP, was found to be associated with an increased chance of early recurrence in BC [29].

CAF chemotherapy alone reduced significantly (p<0.001) segmental (i.e., head, arms, trunk, ribs, spine, pelvis, and legs) and total BMD as compared to the initial state and Healthy Controls, as shown in **Figure 1**. However, CAF + Vitamin D adjunct treatment was responsible for a significant (p<0.05) increase in segmental and total BMD as compared to the initial state. Vitamin D deficiency is associated with secondary hyperparathyroidism, which results in increased bone resorption, the release of Ca from bones, and may precipitate or exacerbate osteoporosis with consequent ill effects on BMD. Osteopenia and osteoporosis in BC patients were found primarily due to early menopause and vitamin D deficiency and later amplified by chemotherapy and endocrine therapy, particularly the aromatase inhibitors [7]. Thus, BC patients must undergo a baseline metabolic bone evaluation with serum vitamin D levels and BMD [7,8].

Previous findings suggest an increased incidence and more aggressive BC tumor characteristics, associated with higher prediagnostic serum Ca levels [30]. BC makes Ca leak out into the bloodstream from bones, thus elevating its levels in the blood. It may also affect the amount of Ca that the kidneys are able to get rid of. Chemotherapy decreases Ca levels in breast and lung cancer patients probably by reducing PTH related peptide levels [31]. Vitamin D helps in Ca absorption in the intestine in the presence of PTH. If vitamin D is not sufficient for that process to happen Ca not completely absorbed and it causes first hyperthyroidism. Thus, when we use CAF chemotherapy adjunct to vitamin D supplementation it causes Ca be absorbed more in bone and increase BMD, which is in line with our findings shown in **Figure 1**. Vitamin D is needed for the body to take in phosphate. Vitamin D and PTH regulate phosphate metabolism, it is suggested that they are both related to cancer incidence thus, their abnormal levels may be responsible for the association between phosphate and

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cancer risks [32,33]. Previous studies showed that P is inversely correlated with BC risk [34].

Conclusions

Albeit the tremendous progress achieved in BC treatment, it is still the principal cause of cancer death among the female population worldwide. Vitamin D is one of the critical factors for female reproductive health, which may have protective effects against many cancer types, including BC. In the present study, we found that vitamin D [25(OH)D] has decreased the risk of BC recurrence by lowering serum levels of tumor marker CA15-3 and some associated risk factors like body weight and PTH, ALP, and Ca to normal levels, thus increasing segmental and total BMD and decreasing the risk of osteoporosis.

List of Abbreviations

25(OH)D: Vitamin D
ALP: Alkaline Phosphatase
ANOVA: Analysis of Variance
BC: Breast Cancer
BMD: Bone Mineral Density
BMI: Body Mass Index
CA15-3: Tumor Marker CA15-3
Ca: Calcium
CAF: Cyclophosphamide, Adriamycin, and 5-Fluorouracil
DXA: Dual-energy X-ray Absorptiometry
NMBC: Non-Metastatic Breast Cancer
P: Phosphorus
PTH: Parathyroid Hormone
TNM: Tumor, Node, and Metastases

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	EIM	AMH	NMA	GIK	AMB	NAA
Research concept and design	✓	--	--	--	--	✓
Collection and/or assembly of data	✓	✓	✓	--	--	✓
Data analysis and interpretation	✓	✓	✓	✓	✓	✓
Writing the article	✓	✓	✓	--	--	✓
Critical revision of the article	✓	--	--	--	--	--
Final approval of article	✓	✓	✓	✓	✓	✓

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