Original Article

Vitamin D Level in Postmenopausal Breast Cancer Patients Before and After Adjuvant Chemotherapy and Endocrine Therapy

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Abstract

Background: Deficiency of vitamin D is associated with the risk of the development of several cancers. **Objective:** This study aimed to verify the effect of the adjuvant chemotherapy and hormonal therapy on the vitamin D level in breast cancer patients. **Materials and Methods:** This is a prospective case–control study consisting of 65 postmenopausal patients with breast cancers compared to 40 postmenopausal control women from Nineveh province, vitamin D level was measured at the time of the diagnosis; immediately after the completion of adjuvant chemotherapy and 6 months after completing chemotherapy attending Mosul oncology Hospital during 2017–2019. **Results:** The present study demonstrated that vitamin D level at the time of diagnosis was lower in patients group compared with the control group. After the completion of adjuvant chemotherapy, the mean value of vitamin D level was significantly lower than the mean value of vitamin D level at the time of diagnosis. Six months after finishing chemotherapy, the value of vitamin D level was slightly recovered but still significantly lower than the mean value of vitamin D level at the time of diagnosis of breast cancer patients. **Conclusion:** Vitamin D deficiency seems common among breast cancer patients in Nineveh province, which became more prominent after giving chemotherapy.

Keywords: Breast cancer, chemotherapy, hormonal therapy, vitamin D

Introduction

Vitamin D_3 belongs to the steroid hormone family. It is crucial for controlling bone health.[1] In addition, many immunogenic and antiproliferative effects of vitamin D are seen in the body; one of these activities is promoting apoptosis through the insulin-like growth factor receptor 1-PI3K-Akt-dependent signaling pathway.[2,3] Therefore, the downregulation of vitamin D_3 signaling and related metabolic pathways is suggested to take an important role in tumor growth.[4]

Vitamin D is produced in two forms: D_2 and D_3. D_2 is a plant-derived form (ergocalciferol),[5] whereas under the skin when exposed to ultraviolet-B radiation, 7-dihydroxy cholesterol is converted to the D_3 form (cholecalciferol).[6] The majority of vitamin D_3 (90%) is produced from the endogenous source, under the skin, and both endogenous and exogenous forms undergo hydroxylation by hepatic cells' microsomal and mitochondrial 24 hydroxylases, which are encoded by CYP24A1 to produce 25-hydroxyvitamin D (calcidiol). Further, hydroxylation of 25-hydroxyvitamin D occurs in the proximal convoluted tubule of the kidney to form the biologically active metabolite, 1,25 dihyroxy-vitamin D.[7]

With 2.3 million new cases in 2020, breast cancer is counting 24.5% of all female cancers globally.[8] In Iraq, breast cancer is reported to be the first type of cancer among the top 10 malignant tumors affecting the

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community; forming 19.5% of the total (4996 cases) and 34.3% of malignant neoplasms in Iraqi females (4922 cases) according to the Iraqi Cancer Registry in 2019.[9]

Higher intake or greater levels of serum vitamin D have been linked to a reduced risk of prostate, colon, and breast cancer, according to oncology researchers.[10] And, the vast majority of epidemiologic data indicate the association between high incidence of breast cancer and vitamin D deficiency.[11]

In addition to that, it has been noted that premenopausal women who consume vitamin D_3 and oral calcium had a lower risk of developing breast cancer.[12] In addition, new research revealed that low serum vitamin D_3 levels were linked to poor prognoses, including a higher risk of cancer mortality and recurrence,[13] and it was found that vitamin D_3 deficiency in breast cancer patients is correlated with larger tumor sizes, higher grade, positivity of lymph node, and advanced stage.[14] In this way, enormous researches and a lot of efforts have been directed toward controlling vitamin D_3 deficiency for reducing breast cancer risk.

Although previous numerous studies have examined the association between breast cancer incidence and vitamin D_3 levels, a few studies have examined the effects of adjuvant chemotherapy and/or hormonal therapy on vitamin D_3 levels, which are the points on which this study concentrates and tries to make them clear to Iraqi postmenopausal breast cancer patients.

Materials and Methods

Patient demographics

This is a prospective case–control study that was done on 65 postmenopausal patients with breast cancers compared with a control group of 40 postmenopausal women. The patient group consists of women who were diagnosed histopathologically having carcinoma of the breast, and have no metastasis, no comorbidities, and no morbid obesity after undergoing surgical excision and attending The Mosul Oncology Hospital to receive adjuvant chemotherapy or chemoradiotherapy from January 2017 to February 2019. The exclusion criteria include those patients having a history of chronic medical conditions or metastatic disease in addition to those patients who have a history of consuming some supplements of vitamin D_3 or drugs that interfere with vitamin D_3 measurements. The control group consisted of completely healthy women who attended for regular checking and breast examination, who neither have a history of cancerous diseases, history of previous treatment with chemotherapy nor history of consuming some supplements of vitamin D_3 or drugs that interfere with vitamin D_3 measurements.

Study design and data collection

The local official scientific committee approved the study design. Patient information regarding the personal and sociodemographic data, which include age, parity, menopausal status, place of residence (whether urban or rural areas), education, physical activity, tonics intake, and the tumor stage at the diagnosis, was recorded.

The patients received one of the three protocols of adjuvant chemotherapy according to the NCCN guidelines which were as follows:

First, Adriamycin and Cyclophosphamide (AC) protocol, Second, Adriamycin and Cyclophosphamide followed by Taxan (AC-T) protocol, Third, Cyclophosphamide, Methotrxate and 5 Fluorouracil (CMF) protocol

The AC chemotherapy protocol was given to 9 of 65 patients. The AC-T chemotherapy protocol was given to 32 of 65 patients, whereas the CMF chemotherapy protocol was given to 24 of 65 patients. Hormonal therapy was given to those patients with luminal A and luminal B molecular subtypes according to the NCCN guidelines indication, which consisted of either tamoxifen or aromatase inhibitor (AI).[15]

Just before the start of the adjuvant chemotherapy, vitamin D_3 levels were assessed for the control group and the patient's group as a baseline reading. The second assessment of vitamin D_3 levels, for the patient's group, was done immediately after the completion of adjuvant chemotherapy. The third assessment of vitamin D_3 levels for the patient's group was done 6 months after completing chemotherapy.

Serum vitamin D_3 levels were measured using the Enzyme-Linked Fluorescent Assay technique from bioMérieux SA, France (VIDAS 25 OH vitamin D total). The deficiency of vitamin D_3 was determined as a level of less than 50 nmol/L (<20 ng/mL), the insufficiency of vitamin D_3 was defined as a level between 50 and 72 nmol/L (20–29 ng/mL), and optimal sufficient vitamin D_3 levels were defined between 75 and 100 nmol/L (30–40 ng/mL), according to the reference values of our study's assay and based on recommendations from the Endocrine Society.[16]

Statistical analysis

Using SPSS version 20 (SPSS, New York, USA), data analysis was carried out where the characteristics of the study population were presented as mean ± standard deviation, and frequencies and percentages were used to present the descriptive measurements. An Independent *t* test was used to compare the patients and the control groups concerning the quantitative variables. *P* value of 0.05 was utilized as the significance level for all analyses.

Ethical approval

The study was carried out in conformity with the ethical standards set forth in the Helsinki Declaration. Before a sample was taken, it was done with the patient's verbal and analytical consent. According to the document with the number 173 issued date (29/12/2021), a local ethics

committee evaluated and approved the study protocol as well as the subject information and consent form.

Results

The data of 65 patients with breast cancer and 40 controls were analyzed, in which all the participant women were in postmenopausal status with a mean age of 66 years for the patients' group and 65 years for the control group, and there was no significant difference between the two groups ($P > 0.05$). For the other descriptive features (parity, occupation, and season), there was no significant difference ($P = 0.05$) between the two groups.

Nearly half of the patients (49.2%) have been given a regimen for combined chemotherapy consisting of AC-T, whereas 36.9% of them have been given a regimen for combined chemotherapy consisting of CMF, and 13.8% of them have been given a combination chemotherapy protocol consisting of AC only. After completing the chemotherapy cycles, 28 patients (43.1%) were kept on AI, 26 patients (40%) were kept on Tamoxifen hormonal therapy, whereas 11 patients (16.9%) did not receive any hormonal therapy. Adjuvant radiation therapy was given to half the patients (52.3%).

In this study, deficiency of vitamin D_3 was found in 45 patients (69.4%) and 14 women (35%) of the control group, whereas vitamin D_3 insufficiency was found in 18 patients (27.6%) compared with 17 women (42.5%) in the control group, and sufficient level of vitamin D_3 was found in two patients (3%) compared with nine women (22.5%) in the controls, as demonstrated in Table 1.

The mean serum vitamin D_3 level (baseline reading) for the patients was 16.9 ng/mL, whereas the mean level of serum vitamin D_3 for the controls was 22.6 ng/mL by comparing the two mean values; there was a significant difference with the P value of less than 0.001, as shown in Table 2.

The second assessment of serum vitamin D_3 level was done after completion of adjuvant chemotherapy, which demonstrated a further increase in the percentage of the patient's group who had a deficiency in vitamin D_3 level (95.4%), and the mean serum vitamin D_3 level dropped to 10.1 (SD=2.9) ng/mL which was considerably less than the baseline reading for the patients' group, $P < 0.001$, as shown in Table 3.

The third assessment of serum vitamin D_3 level was done 6 months after finishing chemotherapy, which demonstrated a decrease in the percentage of the patients' group who experienced deficiency in vitamin D_3 level (90.2%) compared with the second assessment with improvement in the mean level of serum vitamin D_3, which was 12 ng/mL, but it was still significantly lower than the baseline reading for the patients' group, $P < 0.001$, as shown in Table 4.

Furthermore, during the second assessment of vitamin D_3 levels for the patients' group, we studied the effect of chemotherapy protocols on the serum vitamin D_3 level. We found that the mean level of serum vitamin D_3 was 9.6 ng/mL for the patients who had received the AC-T protocol ($n = 32$) and was significantly lower than those patients who received the AC protocol only ($n = 9$), in which P value was 0.001, and a mean level of serum vitamin D_3 was 13 ng/mL.

In addition, the patients who received the CMF regimen ($n = 24$) showed a marked difference, in which the mean level of vitamin D_3 serum was 9.6 ng/mL, whereas the mean serum vitamin D_3 level for those patients who received the AC protocol ($n = 9$) was 13ng/mL ($P = 0.05$), whereas there was no significant difference in the mean vitamin D_3 serum level between the patients who received AC-T protocol ($n = 32$) and those who received CMF protocol ($n = 24$), as demonstrated in Figure 1.

At the end of this study and during the third assessment of vitamin D_3 level (6 months after finishing chemotherapy), this study detected the effect of hormonal therapies (tamoxifen and AIs) on serum vitamin D_3 level, in which a significantly higher mean value of vitamin D_3 level was found in breast cancer patients who received tamoxifen compared with those patients who received AI, as hormonal therapy ($P < 0.001$), as demonstrated in Figure 2.

Table 1: Frequencies and percentages of the vitamin D levels between the patients and the control groups

Vitamin D level	Patients group	Control group
	Frequency (%)	Frequency(%)
Deficiency <20 ng/mL	45 (69.4)	14 (35)
Insufficiency (20–30 ng/mL)	18 (27.6)	17 (42.5)
Sufficient (30–40 ng/mL)	2 (3.0)	9 (22.5)
Total	65 (100)	40 (100)

Table 2: Comparison between the mean values of serum vitamin D in the control group and the patients group (baseline reading)

Parameter	Controls ($n = 40$)	Patients ($n = 65$)	P value
	Mean ± SD	Mean ± SD	
Vitamin D concentration (ng/mL)	22.6750 ± 9.94443	16.9538 ± 5.02628	0.000

SD: standard deviation

Table 3: Comparison between the second assessment, after adjuvant chemotherapy, and baseline reading of mean values of serum vitamin D in patients with breast cancer

Parameter	Baseline reading	Second assessment	*P* value
	Mean ± SD	Mean ± SD	
Vitamin D concentration (ng/mL)	16.9538 ± 5.02628	10.1385 ± 2.93085	0.000

SD: standard deviation

Table 4: Comparison between the third assessment, 6 months after receiving adjuvant chemotherapy, and baseline reading of mean values of serum vitamin D in breast cancer patients

Parameter	Baseline reading	Third assessment	*P* value
	Mean ± SD	Mean ± SD	
Vitamin D concentration (ng/mL)	16.9538 ± 5.02628	12.1538 ± 3.91005	0.000

SD: standard deviation

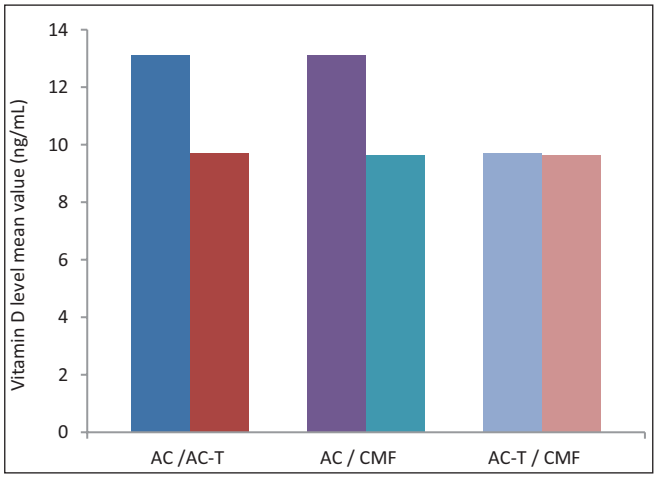

Figure 1: Effect of adjuvant chemotherapeutic protocols on the serum vitamin D level in breast cancer patients. AC: Adriamycin and Cyclophosphamide protocol, (AC-T) Adriamycin and Cyclophosphamide followed by Taxan protocol, CMF: cyclophosphamide + methoterxate + 5 fluorouracil chemotherapy protocol

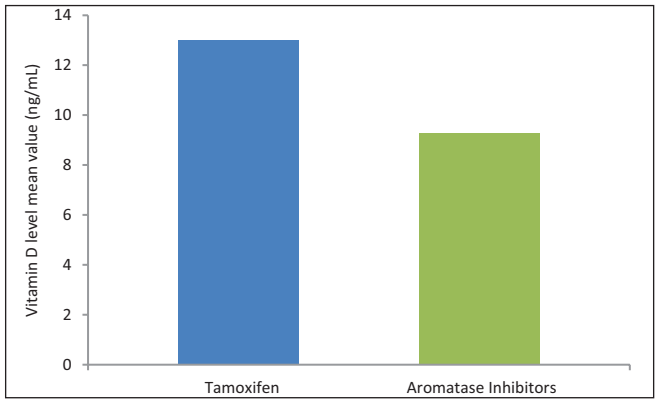

Figure 2: The mean values of vitamin D level in the breast cancer patients who received Tamoxifen and those patients who received AI

Discussion

The present study has been carried out on 65 postmenopausal patients diagnosed to have breast cancers ranging from stage I to stage III compared with 40 healthy women control group in Nineveh province to demonstrate the changes in the levels of vitamin D_3 after completing chemotherapy and 6 months following the end of last cycle of chemotherapy. With or without continuation on hormonal therapy, we reported a significant decrease in the level of vitamin D_3 in the breast cancer patients compared with the control group, which is consistent with the results shown in the previous studies, in which the deficiency of vitamin D_3 level has been associated to breast cancer development,[17,18] and this is mostly related to the antiproliferative and proapoptotic activities of vitamin D_3 in breast cancer cell lines.[19] Vitamin D exerts its action by binding to vitamin D_3 receptor (VDR),[20] which is present in all tissues including the breast and cancer cells, this VDR controls 3%–5% of the human genome.[21] Numerous human genes have specific DNA sequences known as vitamin D response elements that are in charge of producing crucial proteins in the control of cellular proliferation, apoptosis, differentiation, and angiogenesis.[22]

In addition, when we compared vitamin D_3levels for the patient's group before the beginning of adjuvant chemotherapy (baseline reading) with after completion of adjuvant chemotherapy, the present study reported a further decrease in vitamin D_3 levels after completing chemotherapy, which could be attributed to the changes in the lifestyle of these patients who received chemotherapy, which makes them share less outdoor activities and, therefore, experience less sun exposure with lower vitamin D_3 level.[23] Another explanation could be due to poor appetite and decreased oral intake resulting from the common occurrence of mucositis-induced chemotherapy (oral and gastrointestinal), which causes a loss of appetite due to the ulceration, decrease intestinal absorption of vitamin D, diet, and supplements, and subsequent diarrhea.[24] Furthermore, it was found that long-term use of cytochrome P450 (CYP)-inducing agents, which are frequently used to treat cancer patients, can lower vitamin D levels.[25] Since the inducible enzyme CYP3A4, one of the cytochromes P450, is an important source of oxidative metabolism of 1 alpha, 25-dihydroxy vitamin D

in the small intestine and the liver, this could contribute to osteomalacia.[26]

In addition, van Eijk *et al*. suggested that docetaxel, which is one of the chemotherapeutic agents given to the included breast cancer patients, could upregulate the cytochrome CYP3A4 enzyme, so it might change vitamin D's active forms into its inactive metabolites.[27] Furthermore, when compared with healthy mammary epithelial cells, breast cancer cells were shown to have more stable CYP24 mRNA, which is necessary for the elimination of the active metabolite of vitamin D.[28] Similar results have been reported in a study on vitamin D_3 levels in breast cancer patients published by Kim *et al*.[29] showed a decrease in the level of this vitamin after chemotherapy. Similarly, Gabr[20] and Charehbili *et al*.[30] reported a further decline in the vitamin D level after chemoradiotherapy. In contrast, Kim *et al*.[31] found that vitamin D level was still in the deficient state in patients with breast cancer, after completion of neoadjuvant chemotherapy.

A further assessment of vitamin D_3 level (6 months after the last chemotherapy) for our patients showed a slight improvement in the vitamin D_3 level compared with the second assessment (after completion of adjuvant chemotherapy), which is quite plausible as cessation of chemotherapy administration would result in improvement in the patient's general health. Their lifestyles show some changes especially their appetites, an increase in their physical activities, a more sharing of outdoor activities, and sun exposure; in addition to the improvement in the chemotherapy-induced oral and intestinal mucositis.[32] A similar result was reported by Kok *et al*.[33] in their study on 95 breast cancer patients, who discovered that 6 months after treatment ended, serum vitamin D levels had reverted to those seen in healthy women without malignant tumors. Furthermore, they threw light on the potential changes in the vitamin D pathway in breast cancer cells, including the stimulated action of the CYP24 enzyme, dysregulation, and altered levels of VDR gene expression during breast cancer development, as well as potential increased needs of breast cancer cells. The same findings were made by Kim *et al*.[29] who found that serum vitamin D3 levels in 93 breast cancer patients receiving adjuvant chemotherapy decreased in the first 6 months after surgical excision but then rose 12 months later.

Regarding the effect of different chemotherapy protocols that has been given to the patients on vitamin D3 changes, this study has found a significantly higher level of vitamin D_3 in the patients who have received AC protocol compared with those patients who have received CMF protocol or those patients who have received AC-T protocol, but still lower than the baseline reading of Vitamin D, whereas the mean values between the patients who got the CMF and AC-T protocols did not significantly differ from one another.

Little studies has been done regarding the effect of chemotherapy protocols on Vitamin D level, however, Methotrexate (MTX) was found to be associated with suboptimal vitamin D status and vitamin D deficiency,[34] which could probably be due to MTX-induced oral mucositis.[35] Besides the effect of docetaxel on cytochrome P450 (CYP3A4) enzyme,[27] an additional hypothesis has suggested its direct effect on vitamin D circulating levels, which aggravated the deficiency status of vitamin D3 in breast cancer patients.[36]

Furthermore, during the third assessment of vitamin D_3 level (6 months after finishing chemotherapy), the effects of hormonal therapies (tamoxifen and AI) on vitamin D_3 levels were compared. The study found a significantly higher vitamin D_3 level in breast cancer patients who received tamoxifen than those who received AI.

Adjuvant treatment with AI, in postmenopausal women, makes them more susceptible to the risk of pathological fractures than those patients treated with tamoxifen, and this is due to the negative effect of AI on bones, which makes them more prone to the risk of bone loss and osteoporosis,[37] because they would antagonize estrogen, which has an antiresorptive effect on osteoclasts during bone remodeling.[38] Therefore, The Danish Bone Society will advocate for measuring bone mass density as part of the routine examination program before to the start of adjuvant AI therapy.[39] In addition, Al-Biati *et al*.[40] found a significant negative effect of letrozole (AI) on serum vitamin D_3 levels compared with the positive effect of tamoxifen.

Conclusion

This study concludes that vitamin D_3 deficiency is common among breast cancer patients in Nineveh province, and chemotherapeutic protocols (CMF and AC-T) have a negative effect on vitamin D_3 levels. Furthermore, 6 months after the end of the last cycle of chemotherapy, vitamin D_3 level has been improved. Finally, AIs have resulted in a further decrease in vitamin D_3 levels, in breast cancer patients, than in those patients who continue on tamoxifen. Therefore, the study recommends vitamin D_3 assessment, monitoring, and supplementation for breast cancer postmenopausal patients, especially for those who will be prepared to receive adjuvant chemotherapy and hormonal therapy.

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Conflicts of interest

There are no conflicts of interest.

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