VITAMIN-D, CALCIUM STATUS AND QUALITY OF LIFE IN PATIENTS WITH NEOADJUVANT CHEMOTHERAPY IN STAGE II/III BREAST CANCER; A RANDOMISED CONTROL TRIAL

Brij Mohan Singh Pokhariya [1,a] , **Paras Bhandari** [b] **and Abhinav A. Sonkar** [c]

[a] Assistant Professor, MS General Surgery, Dept. of Surgery, ASMC Fatehpur, [b] Senior Resident, Dept. of Surgery, KGMU Lucknow, [c] Professor & Head Dept. of Surgery, KGMU Lucknow

ABSTRACT Background: Breast cancer is the second most common cancer in the world and the most frequent cancer among women. Medical science advancements have provided us with a multimodality approach to breast cancer treatment, thus increasing overall survival. The choice depends on the stage of the disease, the tumour type and the patient's general health. Among the different approaches, chemotherapy is the treatment to destroy the tumour cell. In oncology research, vitamin D has emerged as the most fruitful issue in the previous decade. Efforts connect it with risk reduction and progression in various epithelial cancers, especially breast cancer. Patients with early-stage (EBC) or locally advanced breast cancer are often treated with chemotherapy and anti-hormonal therapy. **Aim and objective:** To evaluate an association between vitamin D levels at baseline, levels at the end of neoadjuvant chemotherapy and changes in these levels during chemotherapy on quality of life scores. To evaluate the effect of Vitamin D supplementation during chemotherapy in breast cancer patients on, Skeletal Health, Chemotherapy related to fatigue, Chemotherapy related toxicities **Materials and methods: Group I (n=55)**– Chemotherapy with Vitamin D (Calcitriol 60,000 IU weekly) + Elemental Calcium (200 mg) daily. **Group II (n=55)**– Chemotherapy alone***Sample size calculated using formula** $n = [(\sigma_1^2 + \sigma_2^2)X(z\alpha + z\beta)^2]/d^2$. **Results:** from the above result, we conclude that most of the patient with carcinoma breast has insufficient to deficient levels of vitamin D. In our present study post, neoadjuvant chemotherapy vitamin D of all patients of group 1 achieved normal value and almost all patients in group 2 without supplementation turning out to be deficient. There was no significant difference in calcium at chemotherapy between the groups. After neoadjuvant chemotherapy, calcium level was significantly higher in Group I than in Group II. There was a significant increase in calcium levels from before to after in Group I and a decrease in Group II . **Conclusions:** The present study found that vitamin D supplementation can normalise vitamin D without significant side effects. All parameters of quality of life and bone mineral density decreased due to neoadjuvant chemotherapy adding to the morbidity of the disease. In relation to the quality of life, only physical was found to have a significant association with change in vitamin D levels. Further fatigue and pain were reduced in patients supplemented with vitamin D. No effect was seen on emotional, functional and social parameters of quality of life despite vitamin D supplementation.

KEYWORDS Breast cancer, Vitamin D, Calcium

Introduction

Breast cancer ranks as the fifth cause of death from cancer overall [1]. According to studies in India, it has been ranked as number one cancer [2]. Trends of breast cancer in India are now being changed, witnessing more and more patients being diagnosed in the younger age groups(30s&40s); Pink Initiative India(www.breastcancerindia.net) [3]. Medical science advancements have provided us with a multimodality approach to breast cancer treatment, thus increasing overall survival. The choice depends on the stage of the disease, the tumour type and the patient's general health. Among the different approaches,

DOI: 10.5455/ijsm.136-1678026773
First Received: March 5, 2023
Accepted: April 4, 2023
Associate Editor: Ivan Inkov (BG);
[1]Corresponding author: Brij Mohan Singh Pokhariya, Assistant Professor, MS General Surgery, Dept. of Surgery, ASMC Fatehpur; Email; drpokhariya06@yahoo.in; Address; Type 3, Room no-201, ASMC Fatehpur (UP), Pin 212601; Mobile; 8948966172

chemotherapy is defined as the treatment. These chemotherapeutic drugs destroy the tumour cells, preventing them from spreading throughout the body [4]. In oncology research, vitamin D has emerged as the most fruitful issue in the previous decade. Efforts connect it with risk reduction and progression in various epithelial cancers, especially breast cancer [5]. Vitamin D has extended beyond bone health and calcium metabolism [6]. Evidence for an association of vitamin D with breast cancer has been obtained from epidemiological studies that found higher cancer rates in Northern latitudes was related to vitamin D deficiency [7]. However, observational studies examining the association between vitamin D intake or blood levels and cancer risk in general and particular have yielded inconsistent results [8-10]. Recent prospective studies have observed an inverse association between serum hydroxyl-vitamin D (25OHD) levels and risk of breast cancer recurrence and mortality in women diagnosed with breast cancer [11- 12]. Patients with early-stage (EBC) or locally advanced breast cancer are often treated with chemotherapy and anti-hormonal therapy [13]. Such therapies can lead to cancer treatment-induced bone loss due to premature ovarian failure or direct cytotoxic effects of the chemotherapy, causing an increase in skeletal morbidity [14-16].

Moreover, Vitamin D insufficiency affects about 50% of women and even more patients with early breast cancer (EBC) [17-20]. This insufficiency worsens the multifactorial bone metabolism alterations observed in these patients, increasing the osteoporosis risk [21], particularly in women with EBC [17-19]. Vitamin D insufficiency may also contribute to the musculoskeletal pain induced by aromatase inhibitors because of its role in the estrogen-related pathway [22]. Recent models of definitions and concepts of Quality of life related to health are now being applied to breast cancer patients. Validated instruments like questionnaires etc. are used to measure and explore the effects and symptoms of disease and evaluate the Quality of life after treatment [23]. The potentially high scientific and social interests of this project are fully based on the premise that with the increasing incidence of breast cancer and chemotherapy-related adverse reactions we should direct towards minimizing symptoms, relieving suffering and bringing the patient to the best possible health-related quality of life, can be summarized as follows: Scientifically:1- The results of this safe, cost-effective intervention with vitamin D supplementation in patients, to the best of our knowledge, address whether the quality of life for these patients could improve from the survival properties of a normal vitamin D status. 2-To provide evidence-based recommendations for the efficacy of vitamin D supplementation to patients in improving their quality of life. Such a finding could be immediately incorporated into clinical practice due to its low cost and lack of toxicity. Furthermore, if confirmed, these findings should provide a solid basis for the design of prospective, well-powered clinical trials directed at customizing vitamin D supplementation regimens in order to expedite the correction of vitamin D deficiency in patients and, more importantly, ensure the fast improvement of their quality of life.3-The most optimistic outcome would be to change the 'current paradigm' for breast cancer patients for a new customized vitamin D as a co-adjuvant therapy.

Material & Methods

The study was conducted in the Department of General Surgery at King George's Medical University, UP. The subjects for the study were enrolled with written and informed consent with n=55 cases in two groups of breast cancer, each receiving Neo adjuvant chemotherapy.

Inclusion criteria

All newly detected cases of breast cancer of all age groups with Stage II/III who are candidates for Neo adjuvant chemotherapy.

Exclusion Criteria

Patients with a prior radiation/chemotherapy/surgery history.

Time period

One Year Intervention **Group I** (n=55) – Chemotherapy with Vitamin D (Calcitriol 60,000 IU weekly) + Elemental Calcium (200 mg) daily. **Group II** (n=55) – Chemotherapy alone*Sample size calculated using formula $n = [(\sigma_1^2 + \sigma_2^2)X(z\alpha + z\beta)^2]/d^2$.

Randomization method

Patients were randomized into two groups using – computer-generated randomization. We used a coded card in an opaque, sealed, and sequentially numbered envelope for allocation concealment.

Aim and Objective

Do supplementation of vitamin D and calcium have a role in improving the quality of life in patients receiving neoadjuvant chemotherapy for Breast Cancer?

Primary objective

To evaluate an association between vitamin D levels at baseline, levels at the end of neoadjuvant chemotherapy and changes in these levels during chemotherapy on quality of life scores.

Secondary objective

To evaluate the effect of Vitamin D supplementation during chemotherapy in breast cancer patients on Skeletal Health, Chemotherapy related to fatigue, and Chemotherapy related toxicities.

Results and Observations

Group-I: Neo adjuvant Chemotherapy with Vitamin D + Elemental calcium (CEF Regime). Group II: Neo adjuvant Chemotherapy alone.

The present study was conducted in the Department of General Surgery, KG Medical University, Lucknow, to evaluate an association between vitamin D levels at baseline & the end of neoadjuvant chemotherapy and changes in these levels during chemotherapy on quality of life scores.

Table-1 shows the comparison of Vitamin D levels between the groups. The groups had no significant ($p>0.05$) difference in Vitamin D level before chemotherapy. Vitamin D levels became normal in all the patients of Group I and none of the Group II patients after neoadjuvant chemotherapy.

Table-2 shows the comparison of calcium status between the groups. There was no significant ($p>0.05$) difference in calcium before chemotherapy between the groups. However, calcium level was found to be significantly ($p=0.001$) higher in Group I (4.83 ± 0.23) than in Group II (4.21 ± 0.66) after chemotherapy and supplementation in Group 1. In addition, there was a significant ($p=0.001$) increase in calcium levels from before to after in Group I and a decrease in Group II ($p=0.01$).

Table 1 Comparison of Vitamin D levels between the groups.

Time period	*Group I (n=55)*		*Group II (n=55)*		*p-value*[1]
	No.	*%*	*No.*	*%*	
Before					
Deficient	*12*	*21.8*	*9*	*16.4*	*0.60*
Insufficiency	*32*	*58.2*	*37*	*67.3*	
Normal	*11*	*20.0*	*9*	*16.4*	
After					
Deficient	*0*	*0.0*	*48*	*87.3*	-
Insufficiency	*0*	*0.0*	*7*	*12.7*	
Normal	*55*	*100.0*	*0*	*0.0*	

[1]*Chi-square test*

Table 2 Comparison of calcium status between the groups.

Time period	*Group I (n=55)*	*Group II (n=55)*	*p-value*[1]
Before	*4.36±0.32*	*4.49±0.41*	*0.07*
After	*4.83±0.23*	*4.21±0.66*	*0.001**
Mean change	*0.47±0.28*	*-0.28±0.58*	*0.01**
p-value[2]	*0.001**	*0.01**	

[1]*Unpaired t-test, *Significant*

Table 3 Comparison of toxicity profile between the groups.

Time period	*Group I (n=55)*		*Group II (n=55)*		*p-value*[1]
	No.	*%*	*No.*	*%*	
Pain					
Before	*7*	*12.7*	*6*	*10.9*	
After	*3*	*5.4*	*13*	*23.6*	*<0.05**
Fatigue					
Before	*0*	*0.0.*	*0*	*0.0*	
After	*27*	*49.1*	*41*	*74.5*	*<0.05**
Anemia					
Before	*5*	*9.09*	*6*	*10.9*	
After	*12*	*21.8*	*12*	*21.8*	
Neutropenia					
Before	*0*	*0.0*	*0*	*0.0*	-
After	*4*	*7.3*	*3*	*5.5*	*0.69*
LVEF					
Before	*0*	*0.0*	*0*	*0.0*	-
After	*0*	*0.0*	*0*	*0.0*	-
Nausea					
Before	*0*	*0.0*	*0*	*0.0*	-
After	*48*	*87.3*	*48*	*87.3*	*1.00*
Diarrhoea					
Before	*0*	*0.0*	*0*	*0.0*	-
After	*51*	*92.7*	*49*	*89.1*	*0.50*
Alopecia					
Before	*0*	*0.0*	*0*	*0.0*	-
After	*50*	*90.9*	*50*	*90.9*	*1.00*
Liver pain					
Before	*0*	*0.0*	*0*	*0.0*	-
After	*0*	*0.0*	*0*	*0.0*	-

[1]*Chi-square test, *Significant*

Table 4 Comparison of QOL-Physical well-being between the groups.

Time period	*Group I (n=55)*	*Group II (n=55)*	*p-value*[1]
Before	*16.33±2.89*	*17.04±3.43*	*0.24*
After	*14.35±2.62*	*13.53±2.84*	*0.12*
Mean change	*1.98±0.80*	*3.50±0.94*	*0.002**
p-value[2]	*0.001**	*0.0001**	

[1]*Unpaired t-test, *Significant*

Table 5 Comparison of QOL-Social/Family well-being between the groups.

Time period	*Group I (n=55)*	*Group II (n=55)*	*p-value*[1]
Before	*16.85±2.20*	*16.67±2.31*	*0.67*
After	*15.67±1.52*	*15.00±2.04*	*0.05*
Mean change	*1.18±2.01*	*1.67±0.66*	*0.11*
p-value[2]	*0.001**	*0.0001**	

[1]*Unpaired t-test, *Significant*

Table 6 Comparison of QOL-Emotional well-being between the groups.

Time period	*Group I (n=55)*	*Group II (n=55)*	*p-value*[1]
Before	*13.76±2.99*	*14.25±3.30*	*0.41*
After	*12.25±2.61*	*12.73±2.97*	*0.37*
Mean change	*1.50±0.57*	*1.52±0.60*	*0.26*
p-value[2]	*0.001**	*0.001**	

[1]*Unpaired t-test, *Significant*

Table 7 Comparison of QOL-Functional well-being between the groups.

Time period	*Group I (n=55)*	*Group II (n=55)*	*p-value*[1]
Before	*15.55±1.98*	*15.07±2.69*	*0.29*
After	*12.04±1.69*	*11.85±2.42*	*0.65*
Mean change	*2.50±0.54*	*3.21±0.59*	*0.08*
p-value[2]	*0.0001**	*0.0001**	

[1]*Unpaired t-test, *Significant*

Table 8 Comparison of QOL-Total score between the groups.

Time period	*Group I (n=55)*	*Group II (n=55)*	*p-value*[1]
Before	*63.25±4.74*	*63.04±7.35*	*0.85*
After	*54.31±4.37*	*53.11±6.20*	*0.24*
Mean change	*8.94±1.25*	*9.92±1.62*	*0.12*
p-value[2]	*0.0001**	*0.0001**	

[1]*Unpaired t-test, *Significant*

Table 9 Comparison of BMD femoral neck (g/cm^2) between the groups.

Time period	*Group I (n=55)*	*Group II (n=55)*	*p-value*[1]
Before	*1.01±0.07*	*0.99±0.09*	*0.19*
After	*0.97±0.04*	*0.96±0.05*	*0.30*
Mean change	*0.03±0.07*	*0.02±0.09*	*0.19*
p-value[2]	*0.10*	*0.15*	

[1]*Unpaired t-test*

Table 10 Comparison of BMD L2-L4 (g/cm^2) between the groups.

Time period	*Group I (n=55)*	*Group II (n=55)*	*p-value*[1]
Before	*1.19±0.04*	*1.18±0.05*	*0.67*
After	*1.13±0.05*	*1.14±0.03*	*0.35*
Mean change	*0.05±0.04*	*0.04±0.05*	*0.26*
p-value[2]	*0.08*	*0.09*	

[1]*Unpaired t-test*

Table 11 Correlation of Vit. D with QOL parameters in Group I.

QOL parameters	*Correlation coefficient*	*p-value*
Physical	*-0.66*	*0.0001**
Social	*-0.22*	*0.10*
Emotional	*-0.09*	*0.50*
Functional	*-0.17*	*0.21*
Total	*-0.36*	*0.007**

**Significant*

Table 12 Correlation of Vitamin. D with QOL parameters in Group II.

QOL parameters	*Correlation coefficient*	*p-value*
Physical	*0.23*	*0.09*
Social	*-0.02*	*0.83*
Emotional	*0.19*	*0.15*
Functional	*0.22*	*0.09*
Total	*0.28*	*0.03**

**Significant*

Table 13 Correlation of Calcium with QOL parameters in Group I.

QOL parameters	*Correlation coefficient*	*p-value*
Physical	*-0.01*	*0.95*
Social	*-0.11*	*0.38*
Emotional	*-0.28*	*0.30*
Functional	*-0.18*	*0.17*
Total	*-0.24*	*0.06*

**Significant*

Table 14 Correlation of Calcium with QOL parameters in Group II.

QOL parameters	*Correlation coefficient*	*p-value*
Physical	*0.13*	*0.33*
Social	*0.03*	*0.79*
Emotional	*0.16*	*0.23*
Functional	*-0.16*	*0.22*
Total	*0.09*	*0.50*

**Significant*

Table-3 compares toxicity profiles between the groups. Again, only pain and fatigue were associated between the groups ($p<0.05$).

Table-4 Shows the comparison of physical well-being QOL between the groups. The groups had no significant ($p>0.05$) difference in physical scores before and after chemotherapy. However, a significant decrease in the physical was found from before to after chemotherapy in both Group I ($p=0.001$) and Group II ($p=0.0001$), with a significantly less change in Group I than Group II.

Table-5 shows the comparison of social/family well-being QOL between the groups. The groups had no significant ($p>0.05$) difference in social score before and after chemotherapy. However, a significant decrease in social score was found from before to after supplementation in both Group I ($p=0.001$) and Group II ($p=0.0001$), with a non-significant mean change between 2 groups

Table-6 shows the comparison of emotional well-being QOL between the groups. The groups had no significant ($p>0.05$) difference in emotional scores before and after chemotherapy. However, a significant decrease in emotional score was found from before to after in both Group I ($p=0.001$) and Group II ($p=0.001$), with a non-significant mean change between the 2 groups.

Table-7 shows the comparison of functional well-being QOL between the groups. The groups had no significant ($p>0.05$) difference in functional score before and after supplementation. However, a significant decrease in emotional score was found from before to after supplementation in both Group I ($p=0.0001$) and Group II ($p=0.0001$), with a non-significant mean change between the 2 groups.

Table-8 shows the comparison of total QOL scores between the groups. There was no significant ($p>0.05$) difference in total QOL score between the groups before and after chemotherapy. However, a significant decrease in total QOL score was found from before to after supplementation in both Group I ($p=0.0001$) and Group II ($p=0.0001$).

Table-9 shows the comparison of BMD femoral neck between the groups. The groups had no significant ($p>0.05$) difference in BMD femoral neck before and after supplementation. In addition, no significant change in BMD femoral neck was found from before to after chemotherapy in both Group I ($p>0.05$) and Group II ($p>0.05$).

Table-10 shows the comparison of BMD L2-L4 between the groups. There was no significant ($p>0.05$) difference between the groups in L2-L4 before and after chemotherapy. In addition, no significant change in L2-L4 was found from before to after chemotherapy in both Group I ($p>0.05$) and Group II ($p>0.05$).

Table-11 shows the correlation between vitamin D change and QOL parameters in Group. The physical score was well correlated with an increase in vitamin D levels. Physical scores significantly decreased before and after supplementation as Vitamin D levels increased ($r=-0.66$, $p=0.0001$). None of the other QOL parameters was correlated with vitamin D levels.

Table-12 shows the correlation of change in vit D and QOL parameters in Group II. None of the QOL parameters was correlated with vit D level in Group II.

Table-13 shows the correlation between calcium change and QOL parameters in Group I. None of the QOL parameters was correlated with calcium levels in Group I.

Table-14 shows the correlation between calcium change and QOL parameters in Group II. None of the QOL parameters was correlated with calcium levels in Group II.

Discussion

The groups had no significant difference in Vitamin D levels before neoadjuvant chemotherapy. However, after neoadjuvant chemotherapy, vitamin D level was significantly higher in Group I (Supplemented with Vitamin D and calcium) than in Group II (no supplementation). There was a significant increase in Vitamin D levels from before to after in Group I and a decrease in Group II, with similar results for calcium also(Table 1&2).In our present study, all patients in group 1 achieved normal values after neoadjuvant chemotherapy vitamin D and calcium status, and almost all patients in group 2 without supplementation were deficient. For toxicities, common terminology criteria for adverse event version 4.0 was used. The chemotherapeutic agent causes fatigue, anaemia, neutropenia, diarrhoea, and vomiting. The present study found that fatigue, anaemia and neutropenia increased in both groups despite supplementation in group 1. However, there was a comparatively less percentage of patients having pain & fatigue in group 1 post-chemotherapy with supplementation. There was no effect of vitamin D on anaemia neutropenia, LVEF (Left ventricular ejection fraction), nausea, diarrhoea, alopecia and liver pain, with almost similar outcomes in both groups before and after supplementation(Table3)(Figure1).

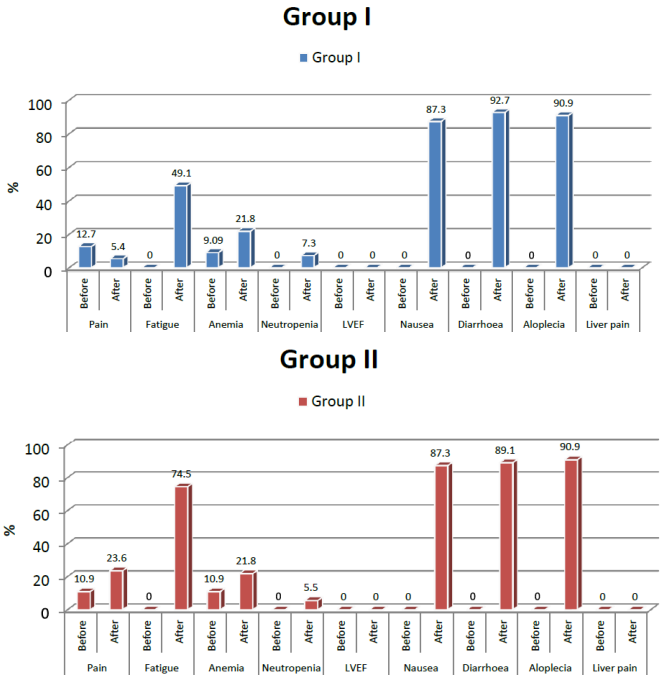

Figure 1 Comparison of toxicity profile between the groups (GROUP -1 and GROUP -2)

The groups had no significant difference in physical score before and after chemotherapy. However, a significant decrease in the physical was found from before to after chemotherapy in both Group I and Group II, with a mean decrease between the two groups after chemotherapy to be significant, suggesting that though the physical quality of life decreases in both the group post-chemotherapy but there is significantly less decrease in patient of group 1 being supplemented with vitamin D(Table4). The groups had no significant difference in social,

emotional and functional scores before and after chemotherapy. However, a significant decrease in their scores was found from before to after chemotherapy in both Group I and Group II, with no significant mean change between the groups, suggesting that vitamin D supplementation has no role in this aspect of quality of life. This quality of life score decreases after chemotherapy in both groups despite vitamin D supplementation in group 1(Table5,6,7,8). There is a decrease in bone mineral density in both groups despite supplementation in group 1 post-chemotherapy but a slightly less change in group 1, which is insignificant.(Table9,10) Lastly, the relationship between change in vitamin D and the quality of life parameter only the physical quality of life parameter was significantly related in group 1. The correlation is negative because the physical quality of life was decreased due to chemotherapy, but there is an increase in vitamin D levels.(Table11,12) The result mentioned above shows a significantly less decrease in physical quality of life in group 1 than in group 2 post-chemotherapy. No other parameters of QOL were significantly related to vitamin D levels in both groups.(Table13,14)

Limitations Of Study

The study has a small limitation - a small sample size, a higher illiteracy rate leading to poor compliance to the questionnaire and patients with locally advanced metastatic disease and undergoing adjuvant chemotherapy was not included.

Conclusion

On the basis of a significant finding of the present study, it is concluded that Vitamin D levels are quite low in breast cancer patients. Vitamin D levels decreased further in patients undergoing neoadjuvant chemotherapy in early breast carcinoma. The present study found that vitamin D supplementation can normalise vitamin D without significant side effects. All parameters of quality of life and bone mineral density decreased due to neoadjuvant chemotherapy adding to the morbidity of the disease. In relation to the quality of life, only physical was found to have a significant association with change in vitamin D levels. Further fatigue and pain were reduced in patients supplemented with vitamin D. No effect was seen on emotional, functional and social parameters of quality of life despite vitamin D supplementation. The study has a small limitation - a small sample size, a higher rate of illiteracy leading to poor compliance to the questionnaire and patients with locally advanced, metastatic disease and undergoing adjuvant chemotherapy were not included. So to improve the study and provide a timely response to patients' Quality of Life, it should be implied on a large group of breast carcinoma patients of all stages receiving neoadjuvant, adjuvant or palliative chemotherapy. It takes an average of 60 seconds longer for the physician/surgeon to extract all of the patient's current problems. Professionals should conduct interviews or semi-structured interviews using electronic assessment methods that are more accurate and less time-consuming. Questionnaires with visual clues and diagrams rather than paper-and-pencil questionnaires will be more compliant.

Author's Contribution

BMS- concept and study design, prepare the first draft of the manuscript, review of data, interpretation of results, revision of the manuscript. **PB-** preparation of manuscript, data collection and analysis, preparation of tables and figures. **AS-** review of manuscript, interpretation of results.

Work Attributed

To- KGMU Lucknow(UP).

Orcid ID

Brij Mohan Singh - https://orcid.org/0000-0002-1805-6200

Paras Bhandari - https://orcid.org/0009-0007-8970-2787

Conflict of Interest

None declared.

Source of Funding

Nil.

Acknowledgment

We would like to thank the authorities of KGMU Lucknow for their support and help.

References

1. Ferlay J, et al F.GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 11.Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr

2. Malvia S et al Epidemiology of breast cancer in Indian women. Asia Pac J Clin Oncol. 2017Aug;13(4):289-295. Doi:10.1111/ajco.12661. Epub 2017

3. STATISTICS OF BREAST CANCER IN INDIA (BREAST CANCER INDIA) http://www.breastcancerindia.net/statistics/trends.html

4. Amy S Clark et al 2014 conducted a laboratory studies that suggests that vitamin D enhances chemotherapy induced cell death.

5. Jawad Obaidi et al Vitamin D and Its Relationship with Breast cancer: An Evidence Based Practice Paper doi:10.5539/gjhs.v7n1p261dx.doi.org/10.5539/gjhs.v7n1p26

6. Goodwin PJ. et al Vitamin D in cancer patients; above all do no harm J ClinOncol2009;27(13):2117-9

7. Garland CF et al Vitamin D for cancer prevention: global perspective. Ann Epidemiol.2009;19(7) 468-83

8. Giovannucci E.: Vitamin D and cancer incidence in the Harvard cohorts. Ann epidemiol 2009; 19: pp. 84-88

9. Davis C.D. and Dwyer J.T.: The "sunshine vitamin": benefits beyond bone? J Natl Cancer Inst 2007; 99:1563-1565

10. Autier P., and Gandini S.: Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled Trial arch InternMed 2007; 167: pp 1730-1737

11. Freedman D.M. et al: Serum levels of vitamin D metabolites and breast cancer risk in the prostate, lung, colorectal, and ovarian cancer screening trial. Cancer Epidemiol Biomarkers Prev 2008; 17: pp. 889-894

12. Goodwin P.J et al: Prognostic effects of 25-hydroxyvitamin D levels in early breast cancer; J Clin Oncol 2009; 27: pp. 3757-3763

13. Brufsky AM.Cancer treatment-induced bone loss: pathophysiology and clinical perspectives; Oncologist 2008; 13: 187-195.

14. Pfeilschifter J, Diel IJ. Osteoporosis due to cancer treatment pathogenesis and management; J Clin Oncol 2000; 18: 1570–1593.

15. Saarto T et al. Chemical castration induced by adjuvant cyclophosphamide, methotrexate, and fluorouracil chemotherapy causes rapid bone loss that is reduced by clodronate: a randomized study in premenopausal breast cancer patients. J Clin Oncol 1997; 15: 1341–1347.

16. Shapiro CL et al : Ovarian failure after adjuvant chemotherapy is associated with rapid bone loss in women with early-stage breast cancer. J Clin Oncol 2001; 19:3306–3311.

17. Crew KD, Shane E, Cremers S et al. High prevalence of vitamin D deficiency despite supplementation in premenopausal women with breast cancer undergoing adjuvant chemotherapy. J Clin Oncol 2009; 27: 2151–2156

18. Tangpricha V, Pearce EN, Chen TC, Holick MF. Vitamin D insufficiency among free living healthy young adults. Am J Med 2002; 112: 659–662 .

19. Peppone et al 2011 Vitamin D deficiency in the patients treated for breast cancer is associated with numerous adverse effects (bone loss, arthralgia, and associated with reduced BMD in the spine.

20. Jacot W, Pouderoux S, Thezenas S et al. Increased prevalence of vitamin D insufficiency in patients with breast cancer after neoadjuvant chemotherapy. Breast Cancer Res Treat 2012; 134: 709–717.

21. Mann GB, Kang YC, Brand Cet al. Secondary causes of low bone mass in patients with breast cancer: a need for greater vigilance. J Clin Oncol 2009; 27: 3605–3610.

22. Khan QJ et al. Effect of vitamin D supplementation on serum 25-hydroxy vitamin D levels, joint pain, and fatigue in women starting adjuvant letrozole treatment for breast cancer. Breast Cancer Res Treat 2010;119:111–118.

23. Delgado-Sanz MC et al: Heath-related quality of life in Spanish breast cancer patients: a systematic review. Health Qual Life Outcomes. 2011; 9: 3.

24. Shin et al. (2002) evaluated the intake of vitamin D, calcium, through dietary consumption to reduce the risk of breast cancer. 88,691 pre and post-menopausal women participated in this study.

25. Lappe, Travers-Gustafson, Davies, Recker, & Heaney (2007) analysed the effect of calcium and vitamin D in reduction of breast cancer. A total of 1180 postmenopausal women were studied.