ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: https://ijrps.com

Serum Levels of 25 Hydroxyvitamin D in Iraqi Women with Breast Cancer: Severity Related Study

Aseel N. Kamil[1], Basil O Saleh*[2], Kifah H Alani[3], Jinan Abdul Kareem Jabbar[4]

[1]Clinical Biochemistry, Ministry of Health, Baghdad, Iraq
[2]Clinical Biochemistry, Department of Biochemistry, College of Medicine, University of Baghdad, Iraq
[3]Clinical Pathology, Department of Pathology, College of Medicine, University of Baghdad, Iraq
[4]MBChB, DMRD, Main Referral Training Center for Early Detection of Breast Tumors/ Oncology Teaching Hospital/Medical City, Bagdad, Iraq

Article History:

Received on: 24.03.2018
Revised on: 09.06.2018
Accepted on: 15.06.2018

Keywords:

25-hydroxyvitamin D (vitamin D),
Tumour marker,
Carcinoma of breast

ABSTRACT

Vitamin D has been found to be one of the principal factors for women reproductive health with protective functions against different tumours. The present study design was aimed to investigate the serum concentrations of 25-hydroxyvitamin D (25(OH) D) and its role in the pathogenesis of breast cancer in Iraqi women. This case study included 38 Iraqi women diagnosed with primary breast cancer (BC). These women were classified according to their severity of BC into group 1 (number=12), group 2 (number=14), and group 3 (number=12). Investigations included serum measurements of 25-hydroxyvitamin D and CA 15-3 by using enzyme-linked immunosorbent assay (ELISA) technique. The study revealed that the mean (±SD) value of serum 25 (OH) D levels were observed to be (16.1±4.30 ng/ml) in the whole group of BC women. The mean value of vitamin D significantly decreased with an advanced stage of BC (p=0.001). The significant negative correlation was found between serum levels of vitamin D and serum levels of CA 15-3 (r=-0.465, p= 0.003). This study concluded the significant role of vitamin D in the pathogenesis of BC and the progression of its severity. Vitamin D doses may be a benefit in the prevention and treatment of breast cancer.

* Corresponding Author

Name: Basil O Saleh
Phone: +9647904407625
Email: basil_omsal@yahoo.com

ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v9i3.1624

Production and Hosted by
IJRPS | https://ijrps.com

INTRODUCTION

Breast cancer (BC) is the most common malignancy in women and the second leading cause of their death from cancer in the world (Alvarado et al. 2012). The most effective way to combat cancer is its prevention and early detection. The tumour marker CA 15-3 (also known as MUC1) is the most commonly investigated parameter in carcinoma of breast follow-up. It is an of high molecular weight membrane glycoprotein, which is usually over transcribed (Domschke *et al.,* 2010; Kim *et al.,* 2010) and aberrantly glycosylated in cancer (Duffy *et al.,* 2000). Till now the measurement of serum CA 15-3 is commonly referred in the assessment of recurrent cancer of the breast and in follow up of chemotherapy in cases of advanced cancer of the breast (Kim *et al.,* 2010; Kumpulainen *et al.,* 2002; Fehm *et al.,* 2002).

Vitamins in general, and particularly D is principal material and has an essential function in minerals homeostasis, skeletal physiology, immune system defences, and growth, development, and maturation of cells (Holick, 2007). The main sources of D are sunlight exposure and also by food and dietary supplementation. Recently, investigations have associated this vitamin lack with pathological complications, like heart and cancer-associated morbidity and mortality (Pilz *et al.,* 2009; Gupta *et al.,*

2011; Hines *et al.,* 2010; Levin *et al.,* 2012). Deficiency of cholecalciferol vitamin levels was found in severe breast cancer stage and recurrent one (Goodwin *et al.,* 2009; Vrieling *et al.,* 2011; Hatse *et al.,* 2012). Cholecalciferol has a key function in bone density, and breast cancer women even with a good prognosis are at high risk for bone demineralization and fractures, mainly because of long-term effects of chemotherapy (Hines *et al.,* 2010; Laird *et al.,* 2010).

Furthermore, deficiency and insufficiency of D levels are correlated with body mass index, and obesity is usually encountered problem among women breast cancer. Also, this pathological deficiency of D is often going undefined by clinicians (Park and Johnson, 2005). For these reasons, low D levels are considered as an important concern in survivors women had breast cancer. This study was aimed to investigate the serum levels of 5(OH) 2 D in Iraqi women with BC and to correlate it with serum levels of proved tumour marker CA 15-3.

Subjects and Methods

This case study was performed at Biochemistry department, Medical School, University of Baghdad and at the Major Center for Early Detection of Breast Tumors/ Medical City, Bagdad, Iraq, during the period from February 2017 to November 2017. Thirty- eight Iraqi women aged (30-65 year) diagnosed by Oncology group to have had breast cancer (BC) were studied. The definition of BC was depended on the triple assessment techniques, i.e., clinical breast examination (CBE), Mammography and Ultrasonography and fine needle aspiration cytology (FNAC) (Al-Alwan and Mualla, 2014). Women with breast cancer of advanced stage (stage IV), multiple types of cancers; female reproductive tract cancers (ovarian, cervical and endometrial cancers), hepatic, renal, colorectal, pancreatic, lung, head and neck tumours were excluded. Also, those women who have had previous cancer (breast or others), smokers and alcoholic women were also excluded from this study. The included women were classified into three groups according to their stage of BC; group 1 (stage I; number=12), group 2 (stage II; number=14), and group 3 (stage III; number=12). The staging of BC was depended on the definition of the International Union against Cancer Tumor-Node-Metastasis (UICC-TNM) classification and the American Joint Committee on the staging of cancer (Edge *et al.,* 2010). The staging procedure was performed using the physical examination and biochemical analysis, mammographic scan, breast mass biopsies and breast/ chest X-rays. Also, a radioisotopic scan of bone, MRI and CT scans were performed when necessary and to exclude metastasis. All the included women have had primary BC that is mean they were not received chemo- or radiotherapy before blood investigations.

Five millilitres (ml.) of the blood sample was aspirated from each woman, and serum was separated after clotting by centrifugation (2500 rpm). The separated serum was stored at – 40°C until the time of measurements of 25 (OH) D and CA 15-3 by using the quantitative sandwich Enzyme-Linked Immunoassay (ELISA) technique. Kits were provided by (HUMAN CO./GERMANY).

The statistical study was achieved by Statistical Package for Social Sciences (SPSS) 20.0.0; p-value was considered significant if <0.05. One-way ANOVA & t-tests performed the statistical study of differences among and between groups. The degree of correlation between the measured parameters within each group was calculated by Spearman's correlation coefficient (r). Results were expressed as mean (±SD).

RESULTS

The mean (±SD) value of the age of the studied BC women was (48.3±9.20 year) and that of body mass index was (29.3±4.1 Kg/m^2). Also, the number of women who were married was 28 (74 %) and single (10; 26 %).

The values of mean serum CA 15-3 and of 25(OH) D of the whole group of BC women and their subgroups of stages are depicted in table 1. The mean value of serum tumour marker CA 15-3 of Iraqi women with BC was found to be (27.3± 18.0 u/ml). The mean value of serum CA15-3 was observed to be increased with advance stage of BC; the level of serum CA15-3 of BC women of group 3 was significantly increased in comparison to that of group 2 and group 1(37.2 ± 7.1 u/ml, 29.2 ± 15.2 u/ml and 15.1 ± 3.9 u/ml; respectively, p<0.005). However, the serum mean value of this tumour marker did not differ significantly between groups 1 and 2 (figure 1). The mean (± SD) value of serum D of the whole group of Iraqi BC women was (16.1±4.3 ng/ml). The mean value of serum D levels significantly decreased with advance BC stages; the serum level of D of group 3 (12.1± 1.50 ng/ml) was significantly decreased compared to that of group 1 (20.3 ± 2.67.1 ng/ml, p=0.001) and group 2 (15.2 ± 3.0 ng/ml, p=0.002). Also, the results revealed a significant decrease (p=0.001) in serum D levels of group 2 compared to that of group 1 (figure 2). The results also showed the significant inverse relationship between serum levels of D and serum CA15-3 (r=- 0.465, p=0.003) as well as the significant positive correlation between serum routine tumour marker CA 15-3 levels and tumour size (r=0.411, p=0.010) (table 2).

Table 1: Mean (±SD) values of serum levels of CA 15-3 and 25 (OH) D in Whole group of BC Women and their Stages

Parameter	Group 1 (Stage I) (number=12)	Group 2 (Stage II) (number=14)	Group 3 (Stage III) (number=12)	A whole group of BC (n=38)
CA 15-3 (u/ml)	(15.1± 3.90)	(29.2±15.20) NS	(37.2 ±7.10) *	27.30± 18.0
25 (OH) D (ng/ml)	(20.3 ± 2.6)	(15.2 ± 3.0 **)	(12.1 ± 1.50**)	(16.1 ± 4.30)

ANOVA and t-test revealed *significant increase in CA 15-3 level in stage III compared to each of stage I & II (p=0.005), NS; non- significant change between stage I & II. **significant decrease in vitamin D level in stage III compared to stage I (p=0.0001) and stage II (p-0.001), the significant decrease in vitamin D level in stage II compared to stage I (p=0.002).

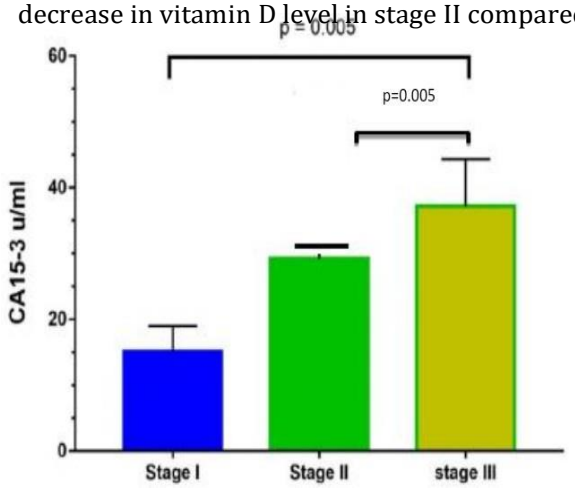

Figure 1: Histogram with an error bar of serum CA15 according to BC stages

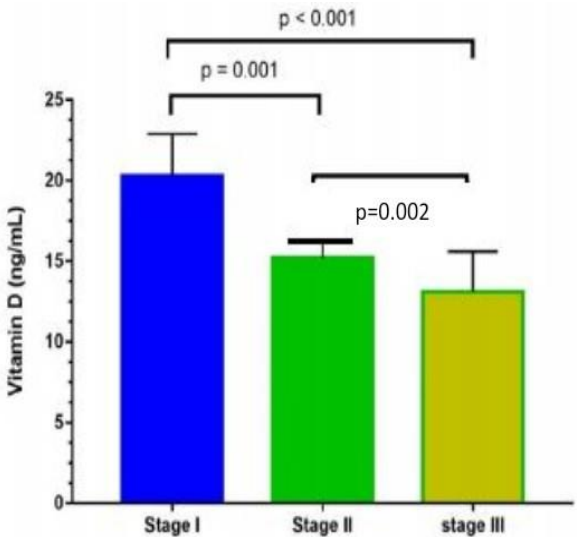

Figure 2: Histogram with an error bar of serum vitamin D according to BC stages

Table 2: Correlation results among the studied parameters

Parameters	CA15-3 (U/ml)	
	r	p-value
Age (year)	-0.257	0.119
BMI (kg/m^2)	-0.209	0.209
Tumour size (cm)	0.411	0.010
Vitamin D (ng/ml)	-0.465	0.003

Linear regression analysis

DISCUSSION

The marker of BC (CA 15-3) is the most commonly investigated laboratory parameter in breast cancer prognosis. First studies pointed that this glycoprotein is elevated in the most of metastatic breast cancer cases and its levels are associated with physical examination abnormalities of breast cancer (Park *et al.,* 2008; Geng *et al.,* 2015). Also, this antigen was found to be an excellent prognostic parameter for monitoring disease development.

In agreement with previous studies (Tarhan *et al.,* 2013; Zang *et al.,* 2013; Vaibhav *et al.,* 2015; Lawicki *et al.,* 2016; Zajkowska *et al.,* 2016; Lawicki *et al.,* 2017), the present study observed that levels of CA 15-3 of BC women with stage III were significantly higher compared to that of stage II and stage I, but without significant change between group I and 2 (table 1). The increased concentrations of tumour factor are related to tumour burden and advanced BC, the high serum CA 15-3 the developed cancer. Our results showed that mean value of D of Iraqi women with BC was found to be (16.1±4.30 ng/ml) which is significantly low as internationally has been considered this level to be insufficient (Ginde *et al.,* 2009). This vitamin and its receptor have interest because of their principal role in the body minerals homeostasis (Holick and Chen, 2008). The interesting was particularly increased when it was concluded they effect significant pathological conditions; CVD, DM, and cancer (Garland *et al.,* 2004; Wang *et al.,* 2008; Pittas *et al.,* 2010). A vast amount of preclinical and epidemiologic researches has concerned with the effect of cholecalciferol on the severity of diseases and mortality, especially cancer. Elevated D levels are linked to low risk of incidence of cancer like the breast. It has been documented that D interfere with proliferation and differentiation of carcinoma cells (Deuster *et al.,* 2017). Also, we found significant decrease of D level with progression the severity of cancer of breast, as women with stage III had the lower value of D compared to less severe stage (stage I and II)., which confirmed previous studies by (Goodwin *et al.,* 2009; Shi *et al.,* 2014)

who suggested that serum vitamin D decreases with more advanced stages of BC. The concerned vitamin has been suggested to ameliorate cell growth of cancer, and investigations have found a negative association between D levels and incidence of breast cancer (Yin *et al.,* 2010). Nutrient D has a potential effect in the prevention of cancer through inhibition of proliferation, differentiation, and cell cycle stabilization (Johansen *et al.,* 2000). The active form of vitamin D is (1, 25(OH) 2 D3), which has a potent inhibitory of effect on a variety of cancer cell types especially breast cancer. The regulatory effects of 1, 25(OH)2 D3 are mediated via the vitamin D receptor (VDR), also a member of the nuclear receptor superfamily. The mechanisms by which 1, 25(OH) 2 D3 exerts its anti-proliferative effects, however, are not clear (Swami *et al.,* 2003). Moreover, the significant negative correlation observed in this study between serum levels of D and CA 15-3 may suggest the high level of D the less severity stage of BC and less possibility of recurrences.

CONCLUSION

Serum level of 25 (OH) D was low in Iraqi women with BC which indicate low body status of this vitamin. Also, the value of D was decreased as the severity of cancer was advance which suggests the potential benefit of D supplementation in the prevention and treatment of BC.

Acknowledgement

The authors would like to introduce their deep thanks to Dr. Tara Farouk, specialists in breast mammography at Major Training Center for Early Detection of Breast Tumors/ Medical City, Baghdad and to Dr. Munawar A Al-Naqqash, College of Medicine, University of Baghdad, Iraq, for their cooperative and assistance in collection and assessment of cases.

REFERENCES

Al-Alwan NAS and Mualla FHF: Promoting Clinical Breast Examination as A Screening Tool for Breast Cancer in Iraq. Iraqi National Journal of Nursing Specialties, 2014; 27 (1).

Alvarado R, Lari SA, Roses RE, Smith BD, Yang W, Mittendorf EA. Biology, treatment, and outcome in very young and older women with DCIS. Ann Surg Oncol. 2012;19:3777–84.

Deuster E, Jeschke U, Ye Y, Mahner S, Czogalla B. Vitamin D and VDR in Gynecological Cancers—A Systematic Review. International Journal of Molecular Sciences. 2017;18(11):2328.

Domschke C, Schuetz F, Sommerfeldt N, Rom J, Scharf A, Sohn C, Schneeweiss A, Beckhove P. Effects of distant metastasis and peripheral CA 15-3 on the induction of spontaneous T cell responses in breast cancer patients. Cancer Immunol. Immunotherapy 2010; 59: 479-486.

Duffy MJ, Sharing S, Sherry F, McDermott E and O'Higgins N. CA 15-3: a prognostic marker in breast cancer Int. J. Biol. Markers, 2000; 15: 330-333.

Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, editors. AJCC cancer staging manual (7th ed). New York, NY: Springer; 2010.

Fehm T, Gebauer G and Jager W. Clinical utility of serial serum c-erbB-2 determinations in the follow-up of breast cancer patients. Treat, 2002; 75: 97-106

Garland CF, Garland F C, Gorham ED, Lipkin M, Newmark H, Mohr SB, Holick M F. The role of vitamin D in cancer prevention. Am. J. Public Health. 2006;96:252–261.

Geng B, Liang MM, Ye X B, Zhao WY. Association of CA 15-3 and CEA with clinicopathological parameters in patients with metastatic breast cancer. Molecular and Clinical Oncology 2015; 3(1): 232–236.

Ginde AA, Liu MC, Camargo CA. "Demographic differences and trends of vitamin D insufficiency in the US population, 1988-2004". Archives of Internal Medicine 2009; 169 (6):626–32.

Goodwin PJ, Ennis M, Pritchard KI, Koo J, Hood N. Prognostic effects of 25 hydroxyvitamin D levels in early breast cancer. J Clin Oncol 2009;27: 3757–3763.

Gupta D, Vashi PG, Trukova K, Lis CG, Lammersfeld CA.Prevalence of serum vitamin D deficiency and insufficiency in cancer: Review of the epidemiological literature. Exp Ther Med 2011;2:181–193.

Hatse S, Lambrechts D, Verstuyf A, Smeets A, Brouwers B, et al. Vitamin D status at breast cancer diagnosis: correlation with tumour characteristics, disease outcome, and genetic determinants of vitamin D insufficiency. Carcinogenesis 2012;33: 1319–1326.

Hines SL, Jorn HK, Thompson KM, Larson JM. Breast cancer survivors and vitamin D: a review. Nutrition 2010;26: 255–262.

Holick M F, Chen T C. Vitamin D deficiency: A worldwide problem with health consequences. Am J Clin Nutr 2008;87:1080s–1086s.

Holick MF. Vitamin D deficiency. N Engl J Med 2007;357: 266–281.

Johansen C, Iversen L, Ryborg A, Kragballe K. 1alpha,25-dihydroxy vitamin D3 induced differentiation of cultured human keratinocytes is accompanied by a PKC-independent regulation of AP-1 DNA binding activity. J Invest Dermatol 2000; 114:1174–9.

Kim MJ, Park BW, Lim JB, Kim HS, Kwak JY, Kim SJ, et al. Axillary lymph node metastasis: CA 15-3 and carcinoembryonic antigen concentrations in fine-needle aspirates for preoperative diagnosis in patients with breast cancer. Radiology, 2010; 254(3): 691-697.

Kumpulainen EJ, Keskikuru RJ, Johansson RT. Serum tumour marker CA 15.3 and stage are the two most powerful predictors of survival in primary breast cancer. Breast Cancer Res Treat 2002; 76: 95–102.

Laird E, Ward M, Mc Sorley E, Strain JJ, Wallace J. Vitamin D and bone health: potential mechanisms. Nutrients 2010;2: 693–724.

Ławicki S, Zajkowska M, Głażewska EK, Będkowska GE, Szmitkowski M. Plasma levels and diagnostic utility of VEGF, MMP-2 and TIMP-2 in the diagnostics of breast cancer patients.Biomarkers. 2017;22(2):157-164.

Ławicki S, Zajkowska M, Głażewska EK, Będkowska GE, Szmitkowski M. Plasma Levels and Diagnostic Utility of M-CSF, MMP-2 and its Inhibitor TIMP-2 in the Diagnostics of Breast Cancer Patients. Clin Lab. 2016;62(9):1661-1669.

Levin GP, Robinson-Cohen C, de Boer IH, Houston DK, Lohman K, et al. Genetic variants and associations of 25-hydroxyvitamin D concentrations with major clinical outcomes. JAMA 2012;308: 1898–1905.

Park BW, Oh JW, Kim JH, Park SH, Kim KS, Kim JH, et al. Preoperative CA 15-3 and CEA serum levels as a predictor of breast cancer outcomes. Park S, Johnson MA. Living in low-latitude regions in the United States does not prevent poor vitamin D status. Nutr Rev 2005;63: 203–209.

Park S, Johnson MA. Living in low-latitude regions in the United States does not prevent poor vitamin D status. Nutr Rev 2005;63: 203–209.

Pilz S, Tomaschitz A, Obermayer-Pietsch B, Dobnig H, Pieber TR. Epidemiology of vitamin D insufficiency and cancer mortality. Anticancer Res 2009;29: 3699–3704.

Pittas A.G., Chung M., Trikalinos T., Mitri J., Brendel M., Patel K., Lichtenstein A.H., Lau J., Balk E.M. Systematic review: Vitamin D and cardiometabolic outcomes. Ann. Intern Med 2010;152:307–314.

Shi L, Nechuta S, Gao Y T, Zheng Y, Dorjgochoo T, et al. Correlates of 25-Hydroxyvitamin D among Chinese Breast Cancer Patients. PLoS ONE 2014;9(1): e86467.

Swami S, Raghavachari N, Muller UR, Bao YP, David Feldman. Vitamin D growth inhibition of breast cancer cells: gene expression patterns assessed by cDNA microarray. Breast Cancer Research and Treatment 2003;80: 49–62, 2003.

Tarhan MO, Gonel A, Kucukzeybek Y, et al. Prognostic significance of circulating tumour cells and serum CA15-3 levels in metastatic breast cancer, single-center experience, preliminary results. Asian Pac J Cancer Prev 2013; 14, 1725-9.

Vaibhav S, Arvind G, Deepak M, Shikha G, Mahajan S. A Prospective Study on Analysis of Ca15-3 in Breast Cancer Patient as a Prognostic Marker. A Prospective Study on Analysis of Ca15-3 in Breast Cancer Patient as a Prognostic Marker. IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) 2015;14; 05-08.

Vrieling A, Hein R, Abbas S, Schneeweiss A, Flesch-Janys D, et al. Serum 25 hydroxyvitamin D and postmenopausal breast cancer survival: a prospective patient cohort study. Breast Cancer Res 2011;13: R74.

Wang T J, Pencina M J, Booth S L, Jacques PF, Ingelsson E, Lanier K, et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation 2008;117:503–511.

Yin L, Grandi N, Raum E, Haug U, Arndt V, Brenner H. Meta-analysis: serum vitamin D and breast cancer risk. Eur J Cancer 2010;46:2196–205.

Zajkowska M, Głażewska EK, Będkowska GE, Chorąży P, Szmitkowski M, Ławicki S. Diagnostic Power of Vascular Endothelial Growth Factor and Macrophage Colony-Stimulating Factor in Breast Cancer Patients Based on ROC Analysis. Mediators Inflamm. 2016;2016:5962946.

Zhang SJ, Hu Y, Qian HL, Jiao SC, Liu ZF, Tao HT, Han L. Expression and Significance of ER, PR, VEGF, CA15-3, CA125 and CEA in Judging the Prognosis of Breast.Asian Pacific J Cancer Prev 2013, 14 (6), 3937-3940.