ORIGINAL ARTICLE

Correlation between Vitamin D Deficiency and Breast Tissue Changes during Child Bearing Age

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ABSTRACT

Background: The role of vitamin D, a steroid hormone that exerts most of its biological activities by binding to the vitamin D receptor, in health and disease is far from understood and the literature is full of contradictory findings. Still, evidence that vitamin D is capable of modulating several features of cancer exist.

Objective: To correlate changes in breast tissue with low serum levels of Vitamin D(Vit D) in females during their reproductive years.

Methods: This study was conducted in the department of Anatomy, Ziauddin Medical College, Karachi and data collected from the department of surgery, Patel Hospital, Karachi in patients undergoing biopsy of the breast lump, between February 2012 and February 2013. 90 patients with diagnosis of breast lump, between 25-40 years of age, with parity varying from 1-5 were divided into 2 groups, those with serum Vit D levels in the normal Range(group A) and those having marked deficiency of serum Vit D levels(group B). Detailed histological study of the biopsy specimen was conducted in all the patients.

Results: Patients who had a marked deficiency of serum vitamin D levels, had more proliferation of stromal connective tissue in group B whereas in group A patients, minimal proliferation of connective tissue was observed in H and E stained slides under the light microscope.

Conclusion: It seems clear that Breast Cancer prevention includes maintaining adequate Vitamin D levels by using oral vitamin D supplementation and with prudent exposure to sunlight.

KEY WORDS: *Breast Lump, Vitamin D, H and E Stain, Serum 25(OH) D, VDR, MAARS Protein.*

Cite as: Wasim B, Hidayat M, Habib F. Correlation between Vitamin D Deficiency and Breast Tissue Changes in During Child Bearing Age. Pak J Med Dent 2014; 3(2):33-37.

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INTRODUCTION

Vitamin D was first identified in 1919 by Edward Mellanby as a lipid soluble substance with anti-rachitic properties and is classically associated with its physiological role of calcium and phosphate regulation in bone metabolism.[1] Humans can obtain vitamin D from two main sources: diet and sunlight exposure. Few natural foods contain vitamin D in significant amounts; among these, fatty fish, eggs and sun-dried mushrooms can be highlighted. Still, the majority (90 to 95%) of the required vitamin D is produced by the skin when exposed to sunlight (ultraviolet B radiation)[2], which has caused vitamin D to be nicknamed 'the sunshine vitamin'.[3] There is a lot of research going on regarding the role of Vitamin D in prevention of a lot of morbid illnesses, Not only has vitamin D been shown to prevent fatal heart attacks, improve survival in kidney diseases, strengthen our bones and prevent and cure depression.[4]

It is a potent weapon against diabetes, rheumatoid arthritis , multiple sclerosis , high blood pressure.[5] Thyroiditis, Crohn's disease and obesity. These have all been linked to low vitamin D levels. Some scientists are call it the magic bullet or the miracle from the sun and recent press has indicated that vitamin D is inversely related to breast cancer.[4]

Vitamin D is a steroid hormone that exerts most of its biological activities by binding to a specific high-affinity receptor, the vitamin D receptor (VDR). VDR belongs to the super family of nuclear receptors for steroid hormones and regulates gene expression by acting as a ligand-activated transcription factor.[6] However, vitamin D can also induce VDR-independent effects, indicated by the fact that the anti-proliferative effects of vitamin D in MCF-7 cells are not exclusively dependent on the presence of the VDR.[7]

Vitamin D is also known to exert rapid effects that are not dependent on gene transcription.[8] Presumably, these effects are mediated by cell surface membrane receptors. Two proteins have been implicated in expression-independent vitamin D action: membrane VDR and the membrane-associated rapid response steroid binding (1,25D3-MARRS) protein.

The role of vitamin D in health and disease is far from understood and the literature is full of contradictory findings. The role of vitamin D in cancer is particularly controversial. Still, evidence that vitamin D is capable of modulating several features of cancer exist. Anti-carcinogenic properties of this hormone include the inhibition of cell proliferation, invasion, metastasis and angiogenesis, and the induction of apoptosis and differentiation.[8]

There is no universally accepted definition of vitamin D deficiency, insufficiency or optimal status. Generally, serum 25-hydroxy vitD (25(OH)**D**) concentrations >50 nmol/l are considered desirable for fracture prevention[9] while levels <25 nmol/l are associated with rickets.[10] Some argue that optimal vitamin D status should be defined at higher 25(OH) D concentrations than 50 nmol/l.[11]

Recommendations for vitamin D supplementation vary based on age and source. Two-thousand international units (2000IU) is noted as the upper limit of safe ingestion.[12] The main marker used in testing for vitamin D deficiency is low serum 25-hydroxy vitamin D [25(OH) D]. The authors report that daily doses of vitamin D need to be higher than the current RDA. Sufficient vitamin D should be taken to elevate 25(OH) D above 30 ng/mL A daily dose of 1,000 IU should do that and not cause toxicity. A serum level of 25(OH) D of 15-20 ng/mL is seen with osteoporosis.

Vitamin D deficiency is associated with increased risk of fractures and is beginning to be associated with increased risk of several types of cancer, including colon, breast, ovarian and prostate cancers.[13]

Recent studies show that certain types of microscopic changes put a woman at higher risk of developing breast cancer. These changes include excessive cell growth or hyperplasia. Hyperplasia can increase the risk of developing breast cancer. Approximately five percent of benign breast biopsies reveal both excessive cell growth, such as hyperplasia, and cells that are abnormal. The location of these abnormal cells can be in the lobules (atypical lobular hyperplasia) or the milk ducts (atypical ductal hyperplasia). A diagnosis of atypical hyperplasia moderately increases breast cancer risk. If a biopsy finds hyperplasia, surgery can remove the abnormal cells.

This study was designed to evaluate the significance of vitamin D in inhibiting the proliferative and cancerous changes in the breast tissue of females in their child bearing age.

METHODOLOGY

This study was conducted in the department of Anatomy, Ziauddin Medical College, Karachi and data collected from the Department of Surgery, Patel Hospital, and Karachi in patients undergoing biopsy of the breast lump, between February 2012 and February 2013.

The experimental protocol was reviewed by the Ethics committee of Ziauddin hospital Karachi. Ninety non-pregnant, non-lactating women who were undergoing biopsy of breast lump, aged between 25–40 years were included, informed consent was obtained from the patients filling questionnaire about participation in our study. All subjects provided blood samples and answered questionnaires about sun exposure and lifestyle. Total serum 25(OH) D was analyzed.

Inclusion criteria for the current study were that subjects had not been pregnant or lactating in the past six months. Of the 150 subjects selected, 90 were eligible for the current study. Non-eligible subjects were excluded due to recent or current lactation. Median parity was 3 children. The patients were divided into 2 groups, each comprising of 45 subjects. Group A comprised of patients having undergone biopsy of a breast tissue for cyst culture, Group B comprised of patients having undergone biopsy for breast lump with a decreased serum level of vitamin D.

Subjects were enrolled from outpatient department. All study visits were conducted in the morning while subjects were fasting. Venous blood samples were drawn and a tissue sample from the biopsy specimen was obtained for histological study via FNAC

RESULTS

The results are shown in Table 1 and Figures 1, 2 and 3.A significant decrease in serum vitamin D levels was observed in group B(4-14ng/ml) as compared to group A patients(30-40ng/ml). Both group A and B patients had a clinical presentation of breast lump, but upon histological grading of the biopsy specimen, proliferation of stromal connective tissue was significantly increased in group B(Figure 1b and 1c),as compared to group A where minimal proliferation of connective tissue was observed under the light microscope(Figure 1a).

Table 1: Females with Breast Lump with or without normal vitamin D level

Parameters	Group A (n = 45) Normal Vitamin D	Group B (n = 45) Vitamin D Deficiency
Age	25-35 years	25-35 years
Breast Lump	positive	positive
Size	2-4cm	2-4cm
Serum Vit D levels	30-40ng/ml	4-14ng/ml
Exposure to Sunlight	1/2-1 hour daily	Less than half an hour daily
Histological Grading	Simple Adenoma	Complex Adenoma (sclerosing-adenosis, ductal hyperplasia)

Figure 1a: Photomicrograph of 5 microns thick H and E stained section from mammary gland of group A patient showing normal amount of connective tissue (fibro glandular). Photomicrograph x 400

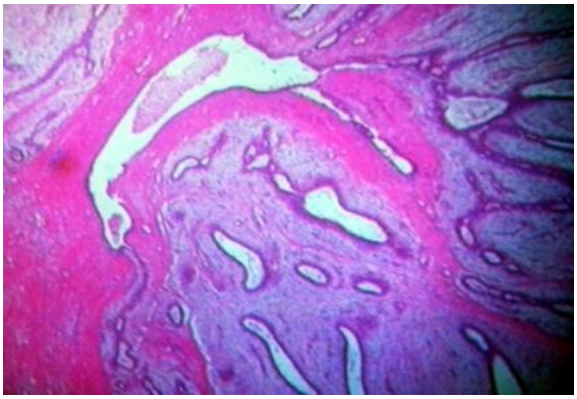


Figure 1b: of 5 microns thick H and E stained section from mammary gland of group B patient showing large amount of fibrous tissue (fibroadenoma). Photomicrograph x 400

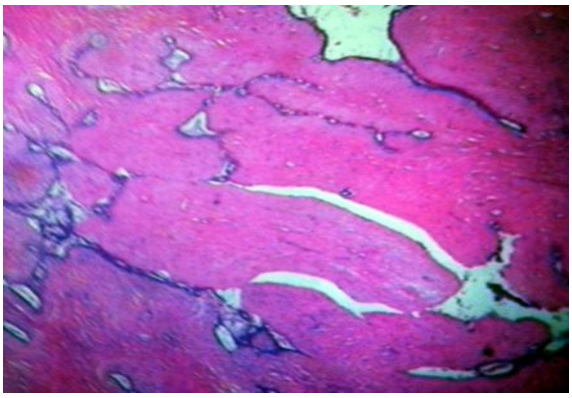
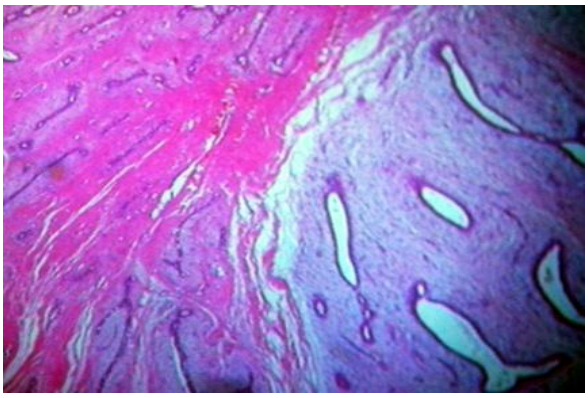


Figure 1c: Photomicrograph of 5 microns thick H and E stained section from mammary gland of group B patient showing large amount of fibrous connective tissue(fibrous hyperplasia). Photomicrograph x 400



DISCUSSION

Poor vitamin D status during pregnancy has been associated with unfavorable outcomes for mother and child. Thus, adequate vitamin D status in women of childbearing age may be important.[13] However the guideline states that for individuals who are vitamin D deficient, higher levels of vitamin D (2000 iu/day for children up to one year of age; 4000 iu/day for children aged 1-18 yrs, and up to 10,000 iu/day for adults aged 19yrs and older recommended. Patients who are pregnant and all those females who are lactating require between 600 IU-1500 iu/day maintaining the ideal blood levels b/w 40-60ng/ml.

Since the linking of vitamin D with breast, colon, prostate and ovarian cancer, we are more concerned with our vitamin D levels. The actual problem arises when we do not have accurate Vitamin D levels, since testing for Vitamin D is expensive, when we have the levels and if they are low we supplement it, but then again we do not recheck the levels and we do not use a maintenance dose. Although we live in a country with plenty of sunlight but we avoid going out in the sun and we cover ourselves with black clothes which reflects the beta radiation of the ultra violet sun rays sun rays so the skin is unable to make vitamin D. The recommended dose is to stay in the sun for half an hour b/w 10-12 am. The best dietary source is cod liver Oil.

In contrast to the extensive studies addressing the expression of Vitamin D signaling and metabolic pathways in breast cancer, the studies in benign lesions of the mammary gland have been ignored.(5) The present study highlighted the significance of vitamin D in inhibiting the proliferation of breast tissue in females of child bearing age who had a marked decrease in the serum levels of vitamin D.

Lopes et al (2012) has evaluated the significance of expression of VDR, CYP27B1 and CYP24A1 in benign breast lesions.[14] Another study described that women with breast cancer.[15] had, on average, lower vitamin D blood levels than women without breast cancer, hence proposing a potential protective effect of vitamin D. In line with this observation, early stage breast cancer patients show higher serum levels of vitamin D than those who have advanced bone metastatic disease and these changes in hormonal levels preceded clinical signs of progression and predicted disease response.[16] Additional evidence is provided by an inverse association between the circulating levels of 25-hydroxyvitamin D3 (the inactive circulating form of vitamin D, which is used to measure the levels of vitamin D in the blood stream) and the risk for developing breast cancer, suggesting that high levels of 25-hydroxyvitamin D3 may be associated with a reduced risk of breast cancer.[17]

CONCLUSION

This study highlights the significance of vitamin D in inhibiting the proliferation of breast lesions

which could be life threatening if not arrested on time. Therefore, supplementing ones diet with vitamin D and obtaining adequate sunlight can prevent women of child bearing age from developing breast lesions.

It seems clear that Breast Cancer prevention includes maintaining adequate Vitamin D levels by using oral vitamin D supplementation and with prudent exposure to sunlight.

REFERENCES

[1] Deluca HF. The Genetics and Biology of Vitamin D. Principles of Medical Biology. 1998; 10: 617–641.

[2] Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr 2004 Dec;80(6 Suppl):1678S-1688S. PubMed PMID: 15585788. Epub 2004/12/09. eng.

[3] Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. K Clin Endocrinol Metab 2011 Jul;96(7):1911-1930. PubMed PMID: 21646368. Epub 2011/06/08. eng.

[4] Garland CF, Gorham ED, Mohr SB, Grant WB, Giovannucci EL, Lipkin M, et al. Vitamin D and prevention of breast cancer: pooled analysis. J Steroid Biochem Mol Biol 2007 Mar;103(3-5):708-711. PubMed PMID: 17368188. Epub 2007/03/21. eng.

[5] Garland CF, Garland FC, Gorham ED, Lipkin M, Newmark H, Mohr SB, Holick MF. Role of Vitamin D in Cancer Prevention. Am J Public Health 2006 Feb; 96(2): 252-261.

[6] Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R. Estimates of optimal vitamin D status. Osteoporo Int 2005 Jul;16(7):713-716. PubMed PMID: 15776217. Epub 2005/03/19. eng.

[7] Costa JL EP, van de Wiel MA, ten Berge D, Schmitt F, Narvaez CJ, Welsh J, Ylstra B. Anti-proliferative action of vitamin D in MCF7 is still active after siRNA-VDR knock-down.BMC Genomics 2009.

[8] Deeb KK, Trump DL, Johnson CS. Vitamin D signaling pathways in cancer: potential for anticancer therapeutics. Nat Rev Cancer. 2007 Sep;7(9):684-700. PubMed PMID: 17721433. Epub 2007/08/28. eng.

[9] Hedlund L, Brembeck P, Olausson H. Determinants of Vitamin D Status in Fair-Skinned Women of Childbearing Age at Northern Latitudes. PLoS One 2013; 8(4): e60864.

[10] Ross AC TC, Yaktine AL, Valle HBD. Dietary Reference Intakes for Calcium and Vitamin D. The National Academies Press. 2011.

[11] Mughal MZ. Rickets. Curr Osteoporosis Rep. 2011; 9(4):291–299.

[12] Dietary Reference Intakes for Calcium and Vitamin D. Ross AC, Taylor CL, Yaktine AL, Del Valle HB, editors. Washington DC: National Academy of Sciences.; 2011.

[13] Evans RM. The steroid and thyroid hormone receptor superfamily. Science (New York, NY). 1988 May 13;240(4854):889-895. PubMed PMID: 3283939. Epub 1988/05/13. eng.

[14] Lopes N, Paredes J, Costa JL, Ylstra B, Schmitt F. Vitamin D and the mammary gland: a review on its role in normal development and breast cancer 2012; 14(211).

[15] Janowsky EC, Lester GE, Weinberg CR, Millikan RC, Schildkraut JM, Garrett PA, et al. Association between low levels of 1,25-dihydroxyvitamin D and breast cancer risk. Public Health Nutr 1999;2(3):283-291.

[16] Mawer EB, Walls J, Howell A, Davies M, Ratcliffe WA, Bundred NJ. Serum 1,25-Dihydroxyvitamin D May Be Related Inversely to Disease Activity in Breast Cancer Patients with Bone Metastases. The J Clin Endocrinol Metab 1997;82(1):118-122. PubMed PMID: 8989244.

[17] Bertone-Johnson ER, Chen WY, Holick MF, Hollis BW, Colditz GA, Willett WC, et al. Plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D and risk of breast cancer. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2005 Aug;14(8):1991-1997. PubMed PMID: 16103450. Epub 2005/08/17. eng.