

Serum Vitamin-D and calcium levels in patients with mastalgia presenting to surgical unit of a tertiary care center

Sana Sahar, Tamjeed Gul, Muhammad Ihtesham Khan, Amina gul, Munir Ahmad

Abstract

Objective: To determine serum calcium and vitamin-D levels in patients of mastalgia presenting to surgical unit of tertiary care center in Peshawar.

Materials and Methods: This cross-sectional descriptive study was done in Surgery unit of Khyber teaching Hospital, Peshawar and Mardan Medical Complex, Mardan from January 2021 to June 2022. Female patients presenting to Surgical unit with mastalgia were included in study by non-probability purposive sampling. Breast carcinoma and fibroadenoma cases were excluded from the study. Data regarding age, marital status, lactation status along with serum vitamin-D and calcium levels was noted and analyzed using SPSS version 26. Shapiro-Wilk and Kolmogorov-Smirnov test were used to determine data distribution. Significance of difference between categorical variables was determined by Chi square test. Association between continuous variables was determined by Pearson correlation test for normal data and Spearman correlation test for non-parametric data. Association between dichotomous categorical and continuous variables was determined by point-biserial correlation. A p-value of less than 0.05 was considered statistically significant.

Results: Mean age of 100 female patients included in the study was 31.52 ± 9.78 years (range: 15-52 years). 92(92%) of cases were premenopausal. 80(80%) cases were married. 60(60%) cases were non-lactating. 56(56%) cases had unilateral mastalgia. Serum calcium levels were normal in 80(80%) cases [$\chi^2=9$, $p=0.003$] while serum vitamin-D levels were decreased in 80(80%) cases [$\chi^2=9$, $p=0.003$]. There was non-significant weak negative correlation between age and serum calcium levels [$r_p=-0.202$, $p=0.332$], age and vitamin-D levels [$r_s=-0.97$, $p=0.643$], lactation status and serum calcium levels [$r_{pbi}=-0.236$, $p=0.203$] and between lactation status and serum vitamin D levels [$r_{pbi}=-0.033$, $p=0.877$].

Conclusion: Hypo-vitaminosis D is common in patients presenting with mastalgia. Vitamin-D levels should be advised to all patients presenting with mastalgia.

Keywords: Hypovitaminosis-D, mastalgia, serum calcium, serum vitamin-D.

Introduction:

Mastalgia refers to pain in breast tissue. It is a common symptom in female population that is defined as dull ache or discomfort in breast tissue, commonly in upper outer quadrant.^{1,2} The severity of pain may vary from mild to severe, and can occur throughout the day. It can be unilateral or bilateral, cyclic or non-cyclic. The condition can last for several months before the patient presents. It is a matter of concern for females due to fear of breast cancer and it can

disrupt sleep and work activity of patients thus adding to stress and anxiety to such an extent so as to disrupt quality of life of such patients.^{3,4}

The exact etiology of mastalgia is unknown.^{3,5} However, certain factors like hormonal imbalance and diet have been reported to be the etiological causes.³ Vitamin-D deficiency has been reported to be associated with mastalgia but it is unclear whether it is etiological factor or not.⁶ Currently, there are different treatment options

Received

date: 2nd July, 2022

Accepted

date: 1st April, 2023

Khyber Medical College/
Khyber Teaching
Hospital, Peshawar
S Sahar
MI Khan
A Gul
M Ahmad

Mardan Medical
Complex, Mardan
T Gull

Correspondence:

Dr. Tamjeed Gul
Assistant Professor,
Surgical Unit, Mardan
Medical Complex,
Mardan.
Cell No:+92 000-0000000
email: drtamjeedgul@
bkmc.edu.pk

Table 1: Characteristics of study population

Age	Mean: 31.52±9.78 Median: 36 Range: 15-52 years	
Menopausal status	Pre-menopausal: 92(92%) Post-menopausal: 8(8%)	$\chi^2= 17.6^*$ p= 0.000
Marital status	Married: 80(80%) Unmarried: 20(20%)	$\chi^2= 9^*$ p= 0.003
Lactation status	Not applicable: 24(24%) Lactating: 16(16%) Non-lactating: 60(60%)	$\chi^2= 8.24^*$ p= 0.016
Laterality of mastalgia	Unilateral: 56(56%) Bilateral: 44(44%)	$\chi^2= 0.360^*$ p= 0.549

* chi-square statistic value; considered significant if p value <0.05

Table 2: Serum calcium and vitamin-D levels in study subjects

Serum calcium levels (mg/dl)	Mean: 9.38±0.73	Low: 0(0%)	$\chi^2= 9^*$
	Range: 8-11.04	Normal: 80(80%)	p= 0.003
		High: 20(20%)	
Serum vitamin D levels (ng/ml)	Mean: 26.8±19.8	Low: 80(80%)	$\chi^2=9^*$
	Range: 8.11-78.75	Normal: 20(20%)	p=0.003
		High: 0(0%)	

*chi-square statistic, considered significant if p<0.05

practised for treating mastalgia i.e. NSAIDs, Tamoxifen, steroids, vitamin-A and E supplements. But due to unclear etiology of mastalgia, there is still no recommended treatment guideline available so far.^{3,6}

Mastalgia is a common symptom observed in about two third of patients with underlying breast pathology.^{2,6,7} The prevalence largely depends on ethnicity as it is seen in 5% females in Asian ethnicity while in 60% cases in British females.⁸ Peak age for mastalgia is 20-40 years.⁸ The incidence decreases as the age increases.⁸ It is very rare in post-menopausal females. It is reported that mastalgia affects about 70% female population at some point of their life but only 30% seek medical advice.^{6,8} Severe pain is reported by 15% of females.² 50% of all referrals to breast clinics are of mastalgia.⁹ This is a very huge burden on breast health care providers.

There is little research available about vitamin-D level in patients of mastalgia.³ It is also not

known whether low vitamin-D level is cause of mastalgia or merely a coincidence. Therefore, the current study is done to determine the correlation between mastalgia and levels of vitamin -D and calcium.

Materials and Methods:

This cross-sectional descriptive study was conducted in Surgery unit of Khyber Teaching Hospital, Peshawar and Mardan Medical Complex, Mardan from January 2021 to June 2022. Female patients referred to Surgery unit for workup of mastalgia were included in the study by non-probability purposive sampling. A detailed history was taken by the attending surgeon regarding age of patient, menopausal status, marital status, lactation status and laterality of pain whether bilateral and unilateral. Clinical examination of breast was done by the attending surgeon, inspecting skin changes and palpating for any lumps. Cases suspected of breast carcinoma and fibroadenoma were excluded from the study. Patient were advised serum Vitamin-D and calcium levels. A 2ml venous blood sample was taken in gel tube and sent to Pathology Department. Vitamin-D and calcium levels were determined by latest fully automated Cobas (pure integrated solutions, Roche diagnostics USA) equipment and verified by a Pathologist. Normal levels for serum calcium and vitamin-D were taken as 8.8-10.4 mg/dl and 20-100 ng/ml respectively.^{10,11} Data regarding age, marital status, lactation status along with serum vitamin-D and calcium levels was noted. Kolmogorov-Smirnov test and Shapiro-Wilk test were used to determine data distribution. Data was considered to be normally distributed if p-value was more than 0.05. Association between continuous variables was determined by Pearson correlation test for normal data and Spearman correlation test for non-parametric data. Association between dichotomous categorical and continuous variables was determined by point-biserial correlation. A p-value of less than 0.05 was considered statistically significant.

Results:

100 female subjects were included in the study.

Table 3: Serum calcium and vitamin-D levels with respect to characteristics of study participants

Characteristics	Serum calcium			Chi-square statistic and significance level	Serum vitamin D			Chi-square statistic and significance level
	Low	Normal	High		Low	Normal	High	
Menopausal status								
Pre-menopausal	-	76(76%)	16(16%)	$\chi^2=1.223$	74(74%)	18(18%)	-	$\chi^2=1.233$
Post-menopausal	-	4(4%)	4(4%)	$p=0.269$	6(6%)	2(2%)	-	$p=0.256$
Lactation status								
Not applicable	-	16(16%)	8(8%)	$\chi^2= 1.667$	18(18%)	6(6%)	-	$\chi^2= 1.768$
Lactating	-	16(16%)	0(0%)	$p=0.435$	14(14%)	2(2%)	-	$p=0.443$
Non lactating	-	48(48%)	12(12%)		48(48%)	12(12%)	-	
Marital status								
Married	-	64(64%)	16(16%)	$\chi^2= 0.0$	68(68%)	12(12%)	-	$\chi^2=1.56$
Unmarried	-	16(16%)	4(4%)	$p=1$	12(12%)	8(8%)	-	$p=0.211$
Laterality								
Unilateral	-	44(44%)	12(12%)	$\chi^2= 0.41$	46(46%)	10(10%)	-	$\chi^2=0.44$
Bilateral	-	36(36%)	8(8%)	$p=0.840$	34(34%)	10(10%)	-	$p=0.91$

Table 4: Correlation analysis

Age and serum calcium levels	$r^*=-0.202, p=0.332$
Age and serum vitamin-D levels	$rs^{**}=-0.097, p=0.643$
Lactation status and serum calcium level	$rpbi^{***}=-0.263, p=0.203$
Lactation status and serum vitamin-D levels	$rpbi^{***}=-0.217, p=0.298$

*Pearson correlation coefficient

**Spearman correlation coefficient

***Point-biserial correlation coefficient

The characteristics of the study sample is given in table 1. Serum calcium and vitamin D levels are given in table 2 and 3. Correlation analysis are given in table 4.

Discussion:

In the current research, vitamin-D level was significantly decreased in patients of mastalgia ($\chi^2=9, p=0.003$). There was no significant correlation vitamin-D levels marital status, lactation status, menopausal status and laterality. Similar findings are reported in various studies done so far.^{3,6} To our knowledge, very little data is available regarding mastalgia and low vitamin-D levels.

Vitamin-D is a fat soluble vitamin that regulates calcium and phosphorus levels in body and thus is involved in maintaining bone health.¹² It is obtained from food but major portion is synthe-

sized in skin under the effect of sunlight.^{12,13} Vitamin-D mediates its effect via interaction with vitamin-D receptor (VDR).¹² It is now known that VDR regulates expression of genes involved in pain signaling pathways, showing that vitamin-D may be involved in pain regulation.¹² Pain is a sensory perception of subjective nature and is mediated by multiple signaling pathways.¹⁴

A recent study done in European population has showed that there was significant correlation between diabetic neuropathic pain and low vitamin-D levels.¹⁵ A strong correlation is also reported between bone pain and low vitamin-D level.¹⁶ Multiple studies are done where it was seen that a low vitamin-D level was associated with increasing severity of pain, and that vitamin-D supplementation results in pain relief.¹⁷⁻²¹

However, there is a need to conduct the studies on pain signaling in VDR knockout mouse models to yield more data on involvement of vitamin-D in pain signaling. It is reported that VDR gene is expressed in skin, central and peripheral neurons, spinal cord and brain. This strengthens the theory that vitamin-D is involved in pain signaling pathway.^{12,22-24} Epidermal growth factor receptor (EGFR) and its downstream effectors are known to modulate pain-signaling pathway. It is now known that the EGFR receptor genes

are regulated by the vitamin-D pathway.^{25,26}

Moreover, Vitamin-D is known to modulate opioid receptor activity by effecting transcription of opioid genes like POMC, PDYN, and PENK that code for endogenous opioids in the cerebrum.²⁷ All the data suggest role of vitamin-D in pain signaling pathways.

Conclusions:

Serum vitamin-D levels should be assessed in all patients of mastalgia as the levels are significantly decreased in such patients irrespective of their marital status, lactation status, age and laterality of mastalgia.

Recommendations:

We recommend follow-up studies where patients with low levels of vitamin-D should be followed up for improvement in symptoms after vitamin-D supplementation.

Limitations:

The present study did not follow up patients and hence could not report the improvement of patients after vitamin-D supplementation.

The study also did not consider the history of any multivitamins supplements intake and/or dietary history, and family history of mastalgia, all of which should be considered in further studies.

Acknowledgement:

All glories be to Almighty Allah for helping us complete the research work.

Conflict of interest: None

Funding source: None

Role and contribution of authors:

Sana Sahar, collected the data, references and did the initial writeup.

Tamjeed Gul, collected the data and helped in introduction writing.

Muhammad Ihtesham Khan, helped in the col-

lection of references and discussion writing.

Amina gul, collected the data, references and helped in interpretation of data.

Munir Ahmad, collected the data, helped in result writing and also helped in introduction and discussion writing.

References:

- Mohammed AA. Evaluation of mastalgia in patients presented to the breast clinic in Duhok city, Iraq: Cross sectional study. *Annals of Medicine and Surgery*. 2020;52:31-5.
- Ali AA, Faraj FH. Clinicopathological profile of mastalgia in females: incidence, types, and pathological correlations. a cross-Sectional study. *Annals of Medicine and Surgery*. 2023;85(10):4764-72.
- Thakur N, Dar MY, Bhat SH. To Study Association between Vit D Deficiency and Mastalgia among Patients Visiting Outpatient Department: A Prospective Study. *International Journal*. 2020;3(6):693.
- Brown N, Burnett E, Scurr J. Is breast pain greater in active females compared to the general population in the UK? *The breast journal*. 2016;22(2):194-201.
- Smith RL, Pruthi S, Fitzpatrick LA, editors. Evaluation and management of breast pain. *Mayo Clinic Proceedings*; 2004: Elsevier.
- Li E, Rai S, Rizkalla N, Sintler M, Vishwanath L. Vitamin D supplementation in the treatment of non-cyclical breast pain. *J Pain Relief*. 2018;7(330):2167-0846.1000330.
- Sivarajah R, Welkie J, Mack J, Casas RS, Paulishak M, Chetlen AL. A review of breast pain: causes, imaging recommendations, and treatment. *Journal of Breast Imaging*. 2020;2(2):101-11.
- Tahir MT, Shamsudeen S. Mastalgia. 2020.
- Iddon J, Dixon JM. Mastalgia. *Bmj*. 2013;347.
- Chang S-W, Lee H-C. Vitamin D and health-The missing vitamin in humans. *Pediatrics & Neonatology*. 2019;60(3):237-44.
- Tinawi M. Disorders of calcium metabolism: hypocalcemia and hypercalcemia. *Cureus*. 2021;13(1).
- Habib AM, Nagi K, Thillaiappan NB, Sukumaran V, Akhtar S. Vitamin D and its potential interplay with pain signaling pathways. *Frontiers in immunology*. 2020;11:820.
- Christakos S, Dhawan P, Verstuyf A, Verlinden L, Carmeliet G. Vitamin D: metabolism, molecular mechanism of action, and pleiotropic effects. *Physiological reviews*. 2016;96(1):365-408.
- Habib AM, Okorokov AL, Hill MN, Bras JT, Lee M-C, Li S, et al. Microdeletion in a FAAH pseudogene identified in a patient with high anandamide concentrations and pain insensitivity. *British journal of anaesthesia*. 2019;123(2):e249-e53.
- Shillo P, Selvarajah D, Greig M, Gandhi R, Rao G, Wilkinson I, et al. Reduced vitamin D levels in painful diabetic peripheral neuropathy. *Diabetic Medicine*. 2019;36(1):44-51.
- Holick MF. Vitamin D deficiency. *New England journal of medicine*. 2007;357(3):266-81.
- Kucukceran H, Ozdemir O, Kiral S, Berker DS, Kahveci R, Ozkara A, et al. The impact of circulating 25-hydroxyvitamin and oral cholecalciferol treatment on menstrual pain in dysmenorrheic patients. *Gynecological Endocrinology*. 2019;35(1):53-7.
- Ghai B, Bansal D, Kanukula R, Gudala K, Sachdeva N, Dhatt SS, et al. Vitamin D supplementation in patients with chronic low back pain: an open label, single arm clinical trial. *Pain physician*. 2017;20(1):E99.
- Helde-Frankling M, Höijer J, Bergqvist J, Björkhem-Bergman L. Vitamin D supplementation to palliative cancer patients shows positive effects on pain and infections—results from a matched case-control study. *PLoS One*. 2017;12(8):e0184208.
- Osunkwo I, Ziegler TR, Alvarez J, McCracken C, Cherry K, Osunkwo CE, et al. High dose vitamin D therapy for chronic pain in children and adolescents with sickle cell disease: results of a randomized double blind pilot study. *British journal of haematology*. 2012;159(2):211-5.
- Huang W, Shah S, Long Q, Crankshaw AK, Tangpricha V. Improvement of pain, sleep, and quality of life in chronic pain patients with vitamin D supplementation. *The Clinical journal of pain*. 2013;29(4):341-7.
- Ray P, Torck A, Quigley L, Wangzhou A, Neiman M, Rao C, et al. Comparative transcriptome profiling of the human and mouse dorsal root ganglia: an RNA-seq-based resource for pain and sensory neuroscience research. *Pain*. 2018;159(7):1325.
- Filipović N, Ferhatović L, Marelja I, Puljak L, Grković I. Increased vitamin D receptor expression in dorsal root ganglia neurons of diabetic rats. *Neuroscience Letters*. 2013;549:140-5.
- Tague SE, Smith PG. Vitamin D receptor and enzyme expression in dorsal root ganglia of adult female rats: modulation by ovarian hormones. *Journal of chemical neuroanatomy*. 2011;41(1):1-12.
- Martin LJ, Smith SB, Khoutorsky A, Magnussen CA, Samoshkin A, Sorge RE, et al. Epregrin and EGFR interactions are involved in pain processing. *The Journal of clinical investigation*. 2017;127(9):3353-66.
- Shen Z, Zhang X, Tang J, Kasiappan R, Jinwal U, Li P, et al. The coupling of epidermal growth factor receptor down regulation by 1alpha, 25-dihydroxyvitamin D3 to the hormone-induced cell cycle arrest at the G1-S checkpoint in ovarian cancer cells. *Molecular and cellular endocrinology*. 2011;338(1-2):58-67.
- Poisbeau P, Aouad M, Gazzo G, Lacaud A, Kemmel V, Landel V, et al. Cholecalciferol (vitamin D 3) reduces rat neuropathic pain by modulating opioid signaling. *Molecular Neurobiology*. 2019;56:7208-21.