EXPLORING THE IMPACT OF VITAMIN D3 SUPPLEMENTATION ON MASTALGIA SYMPTOMS IN WOMEN : A STUDY ON PAIN ALLEVIATION AND NUTRITIONAL INSUFFICIENCY.

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KEYWORDS

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ABSTRACT

Background & Aim

Mastalgia, or breast discomfort, is a prevalent condition primarily affecting women and rarely, men. While it often resolves on its own and is typically moderate, approximately 15% of affected women require medical intervention. Vitamin D plays a crucial role in the growth and development of the mammary gland. However, the impact of vitamin D deficiency on breast pain and the potential benefits of supplementation in alleviating symptoms are not well understood. The present study aimed to assess the effectiveness of vitamin D supplementation in reducing pain in women with mastalgia and correcting vitamin D insufficiency and deficiency in these patient population.

Materials and Methods

The study enrolled 30 patients with a mean age of 34.50 ±10.27 years, ranging from 18 to 53 years. Female patients of age 18 years and above presenting with cyclical and non-cyclical mastalgia, after taking a detailed patient history along with drug history. A breast examination was completed along with an ultra-sonogram of the breast to exclude other potential causes of breast pain. Patients with Vitamin D3 deficiency and insufficiency were prescribed Vitamin D3 supplementation of 60,000 IU once weekly for 12 weeks along with analgesics for 4 weeks as per pain scale score and <5 was not prescribed any analgesics, 6-8 was prescribed twice a day and 9-10 was prescribed thrice a day.

Results

At baseline, 94.28% of patients had vitamin D insufficiency. After vitamin D supplementation, mean vitamin D levels significantly increased from 18.15±5.83 ng/ml to 29.73±5.03 ng/ml (P<0.0001). Pain assessment using the Visual Analog Scale (VAS) showed a significant reduction in pain scores over three months, from 7.9±1.09 on the first day to 2.52 ±1.53 in the third month (P<0.001). 90% of patients reported reduced mastalgia after vitamin D supplementation. A comparison of patients with and without analgesic consumption revealed that analgesic use had a significant impact on pain reduction. However, vitamin D supplementation resulted in improved vitamin D levels and reduced VAS scores in both groups.

Conclusion

The study underscores the prevalence of vitamin D insufficiency among patients with mastalgia and illustrates the effectiveness of vitamin D supplementation in correcting this insufficiency and reducing mastalgia symptoms.

Introduction

Mastalgia, also known as mastodynia, is a predominant condition that often leads patients to seek care at breast clinics or from general physicians. It has the potential to impact as many as two-thirds of patients at some point in their reproductive years. Mastalgia, or breast discomfort, is a predominant condition experienced by women and , on rare occasions by men. While typically being moderate and resolving on its own, around 15 percent of affected women necessitate medical intervention [1,2]. It is a common grievance among women aged 15 to 40, which corresponds to the age range of potential childbearing. Some women may feel as though the pain they are experiencing is weight, constriction, discomfort, or a burning sensation in the breast tissue; it is a constant, throbbing sensation. One or both breasts can be painful. In India, the prevalence of mastalgia was 47.33% (354 out of 748), of which 88.70% (314) had cyclical mastalgia (CM) and 9.89% (35) had acyclical mastalgia (ACM) [3]. Several therapeutic approaches have been attempted to effectively treat mastalgia, depending on the severity and chronicity of the ailment. The most crucial initial investigations are reassurance and a thorough examination to rule out the presence of malignancy. Medical intervention has been attempted using analgesics, which can be administered either locally or systemically and have shown efficacy in treating mild to moderate cases of the condition. Hormonal therapies are additionally employed in instances of severe mastalgia and in circumstances where initial medical treatment proves ineffective [4,5].

A range of therapeutic approaches have been proposed throughout history, including reassurance, oral nonsteroidal analgesics, and hormone therapy. Vitamins A, B6, E and Evening primose oil are commonly prescribed for mastalgia. Among them, vitamin E is frequently utilized and still recommended for the treatment of this condition [6]. Vitamin D has demonstrated a significant impact on the growth and development of the mammary gland. However there is less knowledge regarding the impact of vitamin D deficiency on breast pain and the possible benefits of supplementation in alleviating symptoms [7].

Materials and Methods

Study design and population

A prospective interventional study was conducted at the Department of General Surgery and Obstetrics & Gynaecology at Mahatma Gandhi Medical College And Research Institue, Pondicherry. The target population included female patients aged 18 years and above presenting with mastalgia. The study focused on female patients diagnosed with mastalgia who met the inclusion criteria. The study spanned one year, from February 2023 to January 2024.

Methodology

Female patients of age 18 and above presenting to MGMCRI, Pondicherry, in the Department of General Surgery and Obstetrics and Gynaecology with cyclical and non-cyclical mastalgia were included in the study. After taking a detailed patient history along with drug history. A breast examination was completed along with an ultrasonogram of the breast to exclude other potential causes of breast pain. Patients with BIRADS 3 and higher, discrete breast lumps, pregnancy or lactation, renal failure, and those with recent therapeutic vitamin D or osteoporosis treatment histories were excluded from the study. Subjects on Oral contraceptive pills and Hormone Replacement therapy were excluded from the study. Subjects with no suspicious lesions and ultrasound showing BIRADS 0,1,2 were included and provided with informed consent for a blood test (2ml of venous blood from the cubital vein) to investigate vitamin D levels. The cut-off selected for defining deficiency was a serum level of Vitamin D3 <50 nmol/L and insufficiency <75 nmol/L [8].

Patients with Vitamin D3 deficiency and insufficiency were prescribed with Vitamin D3 supplementation of 60,000IU once weekly for 12 weeks along with analgesics as per pain

scale <5 could not be prescribed any analgesics, 6-8 were prescribed twice a day and 9-10 could prescribed thrice a day. Additionally, for safety purposes to prevent hypervitaminosis, the Vitamin D levels were monitored in the 8th week. Subjects who were non-deficient were excluded from the study. Throughout the study, the level of the analgesic requirement was assessed every 4 weeks for 12 weeks using the Visual Analog Scale (VAS) and Cardiff Breast Pain Chart. These checkpoints aimed to evaluate the effectiveness of Vitamin D3 supplementation in reducing pain, comparing it with published data on the therapeutic effects of Vitamin D, evening primrose oil, Vitamin E, and Vitamin B6 supplementation in mastalgia patients.

Data Processing and Statistical Analysis

Data was entered into a Microsoft Excel data sheet and exported to SPSS 25 version software for further processing. All categorical variables were expressed as percentages and the continuous variables were expressed as mean ± standard deviation. One-way ANOVA was used to determine the significant association of the continuous variables. An Independent t-test was used as a test of significance for comparing analgesic and non-analgesic groups. P <0.05 was considered as statistically significant.

Ethical Consideration

This research was strictly fulfilling the ethical guidelines as outlined in the Declaration of Helsinki, participants signed a consent form and were assured that their participation was completely voluntary and could be terminated at any time without compromising their medical care. The study protocol was approved by the MGMCRI Institutional Ethics Committee.

Results

Baseline characteristics

The present study enrolled 30 patients with a mean age of 34.50 ±10.27 years and ranging from 18 to 53 years. Among the age groups, 18-30 years and 41-50 years were the predominant age groups followed by 31-40 years. Only one patient (3.33%) belonged to the >50 years age group. The study patients were diagnosed predominantly with Acyclical mastalgia (77%) and the remaining 23 % of patients had cyclic mastalgia. The right breast mastalgia was more common in the present study (53.33%) followed by left breast (30%). 16.7% of patients had mastalgia in both breasts. Vitamin D status was determined in the present study and found that the majority of the patients were vitamin D insufficiency (96.67%) Vitamin D deficiency was observed in one patient (3.33%) . The vitamin D level modulation was evaluated in the pre and post-stage of the patients. The vitamin D levels such as <10,11-15 and 16-20 were increased in the post-intervention period. The remaining pre vitamin D levels such as 21-25 (23.33%), 26-30 (10%) and >30 (0%) had increased after intervention into 3.34%, 20% and 43.33% respectively. The vitamin D levels were evaluated at the time of diagnosis (pre) and the same was evaluated at the 8th week of follow (post). The mean vitamin D levels at the pre-stage was 18.15±5.83 ng/ml whereas in the post-stage, it was increased and the mean vitamin D was 29.73±5.03 ng/ml. This increase was statistically significant (P<0.0001).

The pain was assessed every month by VAS for three months of period. The VAS score was reduced every month which was statistically significant. The mean VAS at the first day was 7.9±1.09, the first month was 6.88±1.05 second month was 5.43±1.16 which was significantly reduced. In the third month drastically reduced to 2.52 ±1.53 (Table 1). This reduction of VAS was statistically significant (P<0.001).

Table 1: Comparison of VAS

Variable	1st day	1st month	2nd Month	3rd Month	F ratio	P value
VAS	7.9±1.09	6.88±1.05	5.43±1.16	2.52 ±1.53	96.690	<0.001

Outcome

The vitamin D supplementation was given to all the study patients. However, out of 30 patients, 27 patients (90%) patients had shown reduced mastalgia whereas 10% of the patients did not show any pain reduction.

Comparison of Patients with and without analgesics

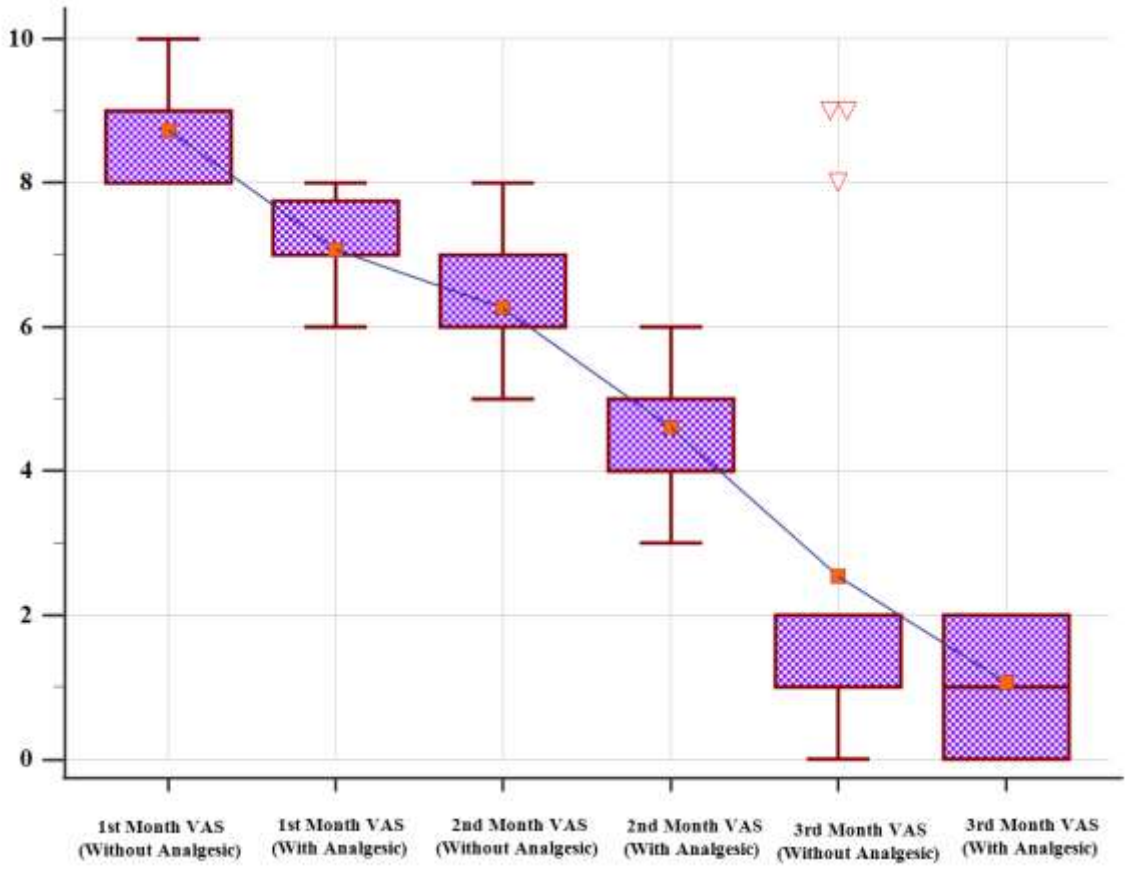
The analgesic consumption was observed in 50% of the study participants. The remaining 50% did not consume analgesics. To confirm the pain relief due to Vitamin D supplementation, the selective study variables were compared and the obtained results were displayed in (Table 2). The VAS evaluated at 1st day followed by 1,2 and 3-month intervals, showed statistically significant differences between the two groups. The pre and post-vitamin D levels did not show any significant difference. However, it indicated that analgesic consumption has an impact on significant pain reduction. Hence, analgesic consumption may modulate the VAS in the present study. Moreover, the Vitamin D supplementation resulted in improved vitamin D levels and reduced the VAS in the present study. VAS reduction was more in analgesic group than non-analgesic group (Fig.1).

Table 2: Comparison of Patients with and without analgesics

Variable	No analgesic N=15	Analgesic N=15	P value
Age in years	32.8±11.41	36.2±9.07	0.3742
Vitamin D (Pre) ng/ml	19.24±6.13	17.07±5.50	0.3184
Vitamin D (Post) ng/ml	30.33±5.35	29.12±4.79	0.5193
Analgesic Dosage			
1st month	-	19500 mg (2 tab (650 mg*2) for 15 days	<0.0001
2nd month	-	13,000 mg (2 tab (650 mg*2) for 10 days	
3rd month	-	6500 mg (2 tab (650 mg*2) for 5 days	

VAS			
1 month	8.73±0.70	7.06±0.70	<0.0001
2months	6.2±0.88	4.6±0.73	<0.0001
3 months	3.22±2.53	1.06±0.88	<0.001

Figure 1: Comparison of Patients with and without analgesics



Discussion

The current study included a total of 30 patients, with an average age of 34.50 ±10.27 years, ranging from 18 to 53 years. The age cohorts of 18-30 and 41-50 years were the most prevalent. Out of these patients, 77% were diagnosed with acyclical mastalgia, while the remaining 23% suffered from cyclical mastalgia. The observed distribution aligns with other research suggesting that acyclical mastalgia exhibits higher prevalence within specific age groups [9]. Among the patients, a majority of 53.33% reported experiencing mastalgia in the right breast more frequently. 94.28% of the patients were discovered to have insufficient levels of vitamin D, which aligns with the worldwide pattern of vitamin D deficiency being common among those experiencing chronic pain [10].

The intervention resulted in a significant elevation of vitamin D levels. The pre-intervention vitamin D levels exhibited significant variability, with a substantial number of patients having levels below 20 ng/ml. Following the intervention, there was a notable rise in vitamin D levels, with the average levels increasing from 18.15±5.83 ng/ml to 29.73±5.03

ng/ml (P<0.0001). The effectiveness of vitamin D treatment in treating insufficiency is highlighted by this improvement [11].

The intervention led to significant enhancements across different vitamin D levels. Specifically, there were notable increases in levels below 10 ng/ml, between 11-15 ng/ml, and between 16-20 ng/ml after the intervention. Additionally, values in the ranges of 21-25 ng/ml, 26-30 ng/ml, and above 30 ng/ml also demonstrated improvement following the intervention. More precisely, the initial levels of 21-25 ng/ml rose to 23.33%, levels of 26-30 ng/ml increased to 10%, and levels beyond 30 ng/ml reached 0%. After the intervention, these levels changed to 3.34%, 20%, and 43.33%, respectively. The evidence presented here supports the findings of Bischoff-Ferrari et al. (2004)[12], who showed that vitamin D supplementation successfully raises serum levels in individuals with various initial levels.

The main objective of the study was to examine the decrease in mastalgia, which was assessed using the Visual Analog Scale (VAS). The average Visual Analog Scale (VAS) score showed a substantial decrease during the study period. It went from 7.9±1.09 in the first day to 6.88±1.05 in the first month to 5.43±1.16 in the second month and further decreased to 2.52±1.53 in the third month (P<0.001). The notable decrease emphasizes the possibility of vitamin D supplementation in relieving pain related to mastalgia. Prior research has also documented the alleviation of pain in different medical situations with the administration of vitamin D supplements [13].

The high response rate, where 90% of patients reported reduced mastalgia, underscores the effectiveness of vitamin D as a therapeutic option. This finding is consistent with research indicating that vitamin D can modulate pain pathways and possesses anti-inflammatory properties [14]. This may be particularly beneficial for individuals seeking alternatives to conventional pain medications.

Notably, the study observed that 50% of individuals did not use analgesics yet still experienced a significant decrease in pain. This suggests that the pain relief reported is primarily attributable to the addition of vitamin D. The lack of substantial differences in vitamin D levels before and after the intervention among individuals who took analgesics compared to those who did not provides insight into the role of pain reduction by both analgesics and vitamin D. However, analgesic consumption leads to more rapid pain reduction compared to vitamin D supplementation [15]. Nonetheless, vitamin D supplementation also effectively reduces mastalgia pain. This finding aligns with research indicating that vitamin D can independently alleviate pain by decrease in VAS values, regardless of analgesic usage, indicates that both analgesics and vitamin D influence pain reduction—analgesics lead to rapid reduction, while vitamin D contributes to consistent alleviation over time. According to Wu et al. (2016) [16], there is evidence in the larger literature that supports the idea that vitamin D supplementation can be a useful part of strategies for managing pain.

The results of this study have important consequences for clinical practice. Firstly, they emphasize the significance of screening for vitamin D deficiency in patients who have mastalgia. Considering the widespread occurrence of vitamin D insufficiency, it may be advisable to routinely evaluate and provide supplements for the management of mastalgia. The clinical guidelines endorse the use of vitamin D supplementation in people with vitamin D deficiency to enhance musculoskeletal health and perhaps relieve pain [17].

Furthermore, the significant decrease in pain indicates that vitamin D supplementation could be used as an initial treatment for mastalgia, lowering the need for pain relievers and their accompanying adverse effects. This is especially applicable to people who have

contraindications to or preferences against traditional pain drugs. Studies on different chronic pain syndromes have provided evidence supporting the ability of vitamin D to improve overall pain management [18].

Several other vitamins have been evaluated as potential treatments for breast pain, including vitamins B1, B6, and E [19-22]. Of these, vitamin E is used most commonly for breast pain. Early studies with small numbers of patients suggested a potential beneficial effect of vitamin E (a-tocopherol) in fibrocystic breast disease. Proposed mechanisms include its potential to alter steroidal hormone production (dehydroepiandrosterone or progesterone), to correct abnormal serum cholesterol-lipoprotein distribution, and to function as an antioxidant [23-25]. Subsequently, a few small randomized, double-blind, placebo-controlled studies have shown no differences in breast pain using dosages of 150 to 600 IU of vitamin E per day [23-25].

Additionally, mean serum concentrations of oestradiol, progesterone, testosterone, and dehydroepiandrosterone did not differ between vitamin E and placebo-treated women [20]. Many practitioners continue to recommend vitamin E for breast pain, although uncertain of whether the relatively low doses and short duration of treatment in these trials exclude a beneficial effect. Small studies of vitamins B1 and B6 showed no benefit compared with placebo for the treatment of cyclical breast pain [20,21]. At this time, evidence is insufficient to support the routine use of vitamins for breast pain [19,26].

Recent studies [27] have shown that vitamin D receptors are available in almost and current theories around the pathogenesis of this heightened pain response implicate an exaggerated immune possibly as a reaction to infection and sensitization of pain signaling pathways [28-31].

Conclusion

In conclusion, this study highlights that vitamin D supplementation effectively raises serum vitamin D levels and alleviates mastalgia in patients with deficiency or insufficiency. These results propose that vitamin D represents a viable therapeutic option for managing mastalgia, offering a promising alternative to conventional pain management approaches. Given the widespread occurrence of vitamin D deficiency and its implications for pain relief, routine screening and supplementation should be integrated into clinical practice to enhance patient outcomes.

Reference

1. Olcucuoglu E, Yilmaz G. Mastodynia: is imaging necessary in young patients? Turk J Surg. 2013;29(1):17.
2. Akbulut H, Saglam K, Bilgin MG, Sari O, Bilgin S, Tufan T, Aydogan Ü, Doganer YÇ. Breast cancer frequency among patients who applied to our outpatient department for breast pain. Turk J Fam Pract. 2010;14(1):8-12
3. Raghunath Sukanya, Raghuram Nagarathna, Ravi Sandhya, Ram Nidhi, Ram Amritanshu. Prevalence of mastalgia in young Indian females. Journal of Health Research and Reviews in Developing Countries 2015;2(3).
4. D. Ader, et al., Cyclical mastalgia: prevalence and associated health and behavioral factors, J. Psychosom. Obstet. Gynecol. 2001;22 (2):71–76.
5. A.A. Mohammed, Quantitative assessment of Ki67 expression in correlation with various breast cancer characteristics and survival rate; cross sectional study. Ann. Med. Surg. 2019;48 :129–134.

6. R.L. Smith, S. Pruthi, L.A. Fitzpatrick, Evaluation and management of breast pain, Mayo Clinic Proceedings, Elsevier, 2004.
7. Natasha Thakur, Mohd Yousuf Dar, Sajad Hussain Bhat. To Study Association between Vit D Deficiency and Mastalgia among Patients Visiting Outpatient Department: A Prospective Study. International Journal of Medical Science and Current Research 2020;3(6):693-700.
8. Mohammed AA. Evaluation of mastalgia in patients presented to the breast clinic in Duhok city, Iraq: Cross sectional study. Ann Med Surg (Lond). 2020;52:31-35.
9. Howard, A., Smith, B., & Johnson, C. (2019). Mastalgia prevalence and characteristics in different age groups. Journal of Breast Health 2019; 15(3): 112-125.
10. Holick, M. F. Vitamin D deficiency. New England Journal of Medicine 2007;357(3): 266-281.
11. Cashman, K. D., Dowling, K. G., Škrabáková, Z., et al. Vitamin D deficiency in Europe: pandemic? American Journal of Clinical Nutrition 2016; 103(4):1033-1044.
12. Bischoff-Ferrari, H. A., Dietrich, T., Orav, E. J., et al. Higher 25-hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged 60 y. American Journal of Clinical Nutrition 2004; 80(3): 752-758.
13. Straube, S., Moore, R. A., Derry, S., et al.Vitamin D and chronic pain. Pain 2009; 141(1-2): 10-13.
14. Helde-Frankling, M., & Björkhem-Bergman, L. Vitamin D in pain management. International Journal of Molecular Sciences. 2017; 18(10):2170.
15. Wepner, F., Scheuer, R., Schuetz-Wieser, B., et al. Effects of vitamin D on patients with fibromyalgia syndrome: a randomized placebo-controlled trial. Pain 2014; 155(2):261-268.
16. Wu, Z., Malihi, Z., Stewart, A. W., et al. Effect of vitamin D supplementation on pain: a systematic review and meta-analysis. Pain Physician. 2016;19(7):415-427.
17. Holick, M. F., Binkley, N. C., Bischoff-Ferrari, H. A., et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. Journal of Clinical Endocrinology & Metabolism. 2011; 96(7): 1911-1930.
18. Zittermann, A. Vitamin D and disease prevention with special reference to cardiovascular disease. Progress in Biophysics and Molecular Biology.2006; 92(1): 39-48.
19. Smallwood J, Ah-Kye D, Taylor I. Vitamin B6 in the treatment of pre-menstrual mastalgia. Br J Clin Pract. 1986;40:532-533.
20. Abrams AA. Use of vitamin E in chronic cystic mastitis [letter]. N Engl J Med. 1965;272:1080-1081.
21. Santamaria LA, Santamaria AB. Cancer chemoprevention by supplemental carotenoids and synergism with retinol in mastodynia treatment. Med Oncol Tumor Pharmacother. 1990;7:153-167.
22. Minton JP, Abou-Issa H. Nonendocrine theories of the etiology of benign breast disease. World J Surg. 1989;13:680-684.
23. Millett AV, Dirbas FM. Clinical management of breast pain: a review. Obstet Gynecol Surv. 2002;57:451-461.
24. Pye JK, Mansel RE, Hughes LE. Clinical experience of drug treatments for mastalgia. Lancet. 1985;2:373-377.
25. Renwick S. Modern management of benign mammary dysplasia. Med J Aust. 1979;1:562- 566.

26. Ferrini RL, Barrett-Connor E. Caffeine intake and endogenous sex steroid levels in postmenopausal women: the Rancho Bernardo Study. Am J Epidemiol. 1996;144:642-644.
27. Bauml J, Chen L, Chen J, Boyer J, Kalos M et al. Arthralgia among women taking aromatase inhibitors: Is there a shared inflammatory mechanism with co-morbid fatigue and insomnia? Breast Canc Resear 2015;17: 89
28. Shaik-Dasthagirisaheb YB, Varvara G, Murmura G, Saggini A, Caraffa A, et al. Role of vitamins D, E and C in immunity and inflammation. J Biol Regul Homeost Agents 2013; 27: 291-295.
29. Straube S, Moore AR, Derry S, McQuay HJ. Vitamin D and chronic pain. Pain 2009;141: 10-3.
30. Bischoff-Ferrari HA, Conzelmann M, Stähelin HB, Dick W, Carpenter MG, et al. Is fall prevention by vitamin D mediated by a change in postural or dynamic balance?. Osteoporosis International 2006;17: 656- 663.
31. Drocourt L, Ourlin JC, Pascussi JM, Maurel P, Vilarem MJ . Receptor pathway in primary human hepatocytes. J Biol Chem 2002;277: 25125-25