Clinical Trial

Vitamin D Supplementation in Patients with Chronic Low Back Pain: An Open Label, Single Arm Clinical Trial

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Background: Vitamin-D deficiency may possibly be related to chronic low back pain (CLBP).

Objective: The study is aimed to assess the impact of vitamin-D supplementation on pain intensity, functional disability, and vitamin-D levels in patients with CLBP.

Study Design: Single arm open-label study.

Setting: Outpatient pain clinic of a tertiary care hospital.

Methods: Sixty-eight eligible patients (CLBP for ≥ 3 months, pain score ≥ 50 on visual analogue scale (VAS) and plasma 25-Hydroxyvitamin D3 levels < 30 ng/mL) were enrolled. Patients were supplemented with 60,000 IU of oral vitamin-D3 given every week for 8 weeks. Efficacy parameters included pain intensity and functional disability measured by VAS and modified Oswestry disability questionnaire (MODQ) scores at baseline, 2, 3, and 6 months post-supplementation. Plasma 25(OH) D3 levels were measured at baseline and 8 weeks.

Results: Baseline mean (SD) vitamin-D levels were 12.8 (5.73) ng/mL and increased to 36.07 (12.51) post supplementation ($P < 0.01$). Forty-five (66%) patients attained normal levels (> 29 ng/mL) post supplementation. Significant reduction in VAS was observed at 2, 3, and 6 months [61 (19), 45 (19), 36 (18)] as compared to 81 (19) at baseline ($P \leq 0.001$ at all-time intervals). A significant improvement in the functional ability was also observed at 2, 3, and 6 months [36 (12), 31 (13), and 26 (10)] as compared to baseline 45 (16) ($P \leq 0.001$ at all-time intervals).

Conclusion: Vitamin-D supplementation in deficient CLBP patients may lead to improvement in pain intensity and functional ability apart from normalization of the levels. Future controlled clinical trials are required to confirm the hypothesis.

Key words: Vitamin D, deficiency, screening, low back pain, chronic, supplementation

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Back pain is the most common pain complaint, second only to headache (1). Chronic low back pain (CLBP) is often progressive and the cause may be difficult to ascertain. Despite the availability of many pharmacological and invasive methods of treatment, many patients still suffer from considerable morbidity (1). Vitamin-D deficiency has been correlated with chronic musculoskeletal pain including low back pain (LBP) (1-4). A high prevalence of vitamin-D deficiency (up to 83%) has been reported in patients with CLBP in comparison to the general population (1-4). The mechanisms

underlying these associations remain unclear (5,6). Theoretically, 2 possible links have been postulated. Firstly, the diffuse pain in bones and muscles, weakness, and paresthesia may be caused by hypovitaminosis D. Secondly, hypovitaminosis D could play a role in the development of modic changes via the increased susceptibility to inflammation in the vertebral end plates (7).

The prevalence of vitamin-D deficiency is found to be 50% – 90% on the Indian subcontinent and is attributed to low dietary intake along with skin color and changing lifestyle despite the availability of ample sunlight (8). Evidence on the efficacy of vitamin-D supplementation in symptom improvement in chronic pain including CLBP is conflicting. A randomized clinical trial conducted in an Iranian population reported inefficacy of vitamin-D supplementation in non-specific LBP patients (9).

The present study is performed with an aim to assess the efficacy and safety of vitamin-D3 supplementation in improving pain and other outcomes in CLBP patients having below normal vitamin-D levels.

Methods

Study Design and Population

This single arm, open label study was conducted in a pain clinic of a public tertiary care hospital in India after obtaining approval from the Institute ethics committee (PGIMER, Chandigarh, India). Patients were recruited from January 2013 to July 2014. The trial was registered with the Clinical Trial Registry of India (CTRI/2014/03/004459). The study was funded by Department of Science and Technology, UT Chandigarh, India.

The study site is located in northern India (Chandigarh) which has a humid subtropical climate that is mild with dry winters, hot humid summers, and moderate seasonality. Every year, the clinic provides a comprehensive diagnostic evaluation for approximately 1000 new patients with various pain conditions.

Inclusion Criteria

Patients of either gender, aged 18 – 75 years with CLBP for ≥ 3 months, with or without leg pain not responding to medications and physical therapies, having a pain score of at least 50 as assessed on 0 – 100 visual analogue scale (VAS) at baseline, and having low plasma 25-Hydroxyvitamin D3 levels (< 30 ng/mL) were eligible for study recruitment. The diagnosis of CLBP was established based on signs and symptoms and investigations like magnetic resonance imaging (MRI).

Patients were required to have stable pain score for 3 months before recruitment and could be on any oral analgesic therapy. The patients were also required to have fluency in English, Hindi, or Punjabi in order to complete the baseline pain related questionnaire. The questionnaires included VAS to measure CLBP intensity, functional disability using Modified Oswestry disability questionnaire (MODQ), work status, and the prior use of medications.

Exclusion Criteria

Patients were excluded if they had evidence of other causes of neuropathy or painful conditions like diabetes mellitus, rheumatoid arthritis, and symptomatic osteoarthritis of the hip, knee, and ankle. Patients diagnosed with epilepsy, psychiatric diseases, and substance abuse, metabolic bone disease (hypo- or hyperparathyroidism), chronic renal disease, and medical or surgical disorders affecting vitamin-D metabolism (gastric surgery, chronic liver disease, renal failure, intestinal malabsorption, systemic infection, cancers, etc.) were also excluded. Patients consuming drugs altering bone metabolism like corticosteroids or bisphosphonates, pregnant and lactating mothers, and women intending to be pregnant were also excluded. Patients taking vitamin-D supplements during the past 3 months were also excluded from the present study.

Measurement of Plasma Vitamin-D Levels [25-Hydroxyvitamin D (25(OH) D3)]

After an overnight fasting, a blood sample was taken. Plasma 25(OH) D3 levels were measured by electrochemiluminescence immunoassay (ECLIA) on an automated analyzer (ELECSYS-2010), using kits supplied by Roche Diagnostics (Germany). This technique provides a broad measuring range and high precision at the low end of detection to aid in the assessment of deficient patients. All the blood samples were collected between 9:00 AM and 10:00 AM to prevent any circadian variation.

Definition of Vitamin-D Levels

According to the level of 25(OH) D3, vitamin-D deficiency was defined as a 25(OH) D3 level of ≤ 20 ng/mL, vitamin-D insufficiency as > 20 – 29 ng/mL, and normal level as > 29 ng/mL (10). Further, severity of vitamin-D deficiency was grouped as follows: ≤ 4 ng/mL profound deficiency; 5 – 8 ng/mL severe deficiency; 9 – 12 ng/mL

moderately severe deficiency; 13 – 16 ng /mL moderate deficiency; and 17 – 20 ng/mL marginal deficiency (11).

Study Procedure

All new patients referred to the pain clinic during the data collection period were screened for eligibility criteria including fasting plasma 25(OH) D3 levels. Eligible patients providing written informed consent were enrolled. At enrollment, a baseline evaluation of disease activity was performed by a pain physician/study investigator. All the information was recorded in a structured case record form. Baseline evaluation included sociodemographic characteristics including age, gender, education, smoking, and alcoholic status as assessed through a direct patient interview. Height and weight were measured to calculate body mass index (BMI), and categorized as < 18.4, 18.5 to 24.99, 25 to 29.99, and ≥ 30 kg/m^2, which are the cut-off points for underweight, normal, overweight, and obesity (12) (Table 1).

Treatment Regimen

Induction Phase

Active vitamin-D3 sachet in a dose of 60,000 IU every week orally for a period of 8 weeks was given to the enrolled patients. Patients having serum vitamin-D level < 5 ng/mL were given 60,000 IU daily orally for the initial 5 days and then 60,000 IU every week for the next 8 weeks. The vitamin-D level was repeated at the end of induction therapy. If the vitamin-D level remained below < 29 ng/mL at this point, then the similar treatment regimen was repeated as mentioned above.

Maintenance Phase

The patients achieving normal levels of vitamin D after induction therapy were put on maintenance therapy. This consists of 60,000 IU orally every month given for next 6 months. Treatment was stopped for the patients who achieved serum vitamin-D level > 60 ng/mL.

Mode of Supplementation

Patients were advised to take the active vitamin-D3 sachet containing 60,000 IU orally by mixing in a glass of milk early morning every week.

Efficacy Endpoints

Study endpoints included plasma 25(OH) D3 levels after completion of 8 weeks of the induction phase of vitamin-D supplementation, change in pain score from baseline as measured by VAS, disability as measured by MODQ, and drug tolerability. Proportion of patients achieving effective pain relief (EPR), defined as ≥ 50% reduction in pain score from baseline as assessed on VAS at 3 months, was also calculated. Patient characteristics and outcome measures were collected at baseline, 2, 3, and 6 months post supplementation.

Table 1. *Baseline characteristics (n = 68).*

Parameter		Value
Age (Yr)	Mean (SD)	44 (12)
Male	N (%)	37 (55)
BMI*	Mean (SD)	25.8 (3.7)
Smoking	N (%)	12 (18)
Alcohol	N (%)	8 (12)
Duration of low back pain (Months)	Median (IQR)	36 (13-96)

*BMI, body mass index

Statistical Analysis

Patient characteristics and baseline and follow-up parameters were expressed in mean and standard deviation (SD), numbers and percentage (%), and median and interquartile range (IQR). Baseline and follow-up VAS, MODQ, and plasma 25OHD were analyzed using a paired student t-test. Proportion of patients achieving plasma 25OHD level normalization after supplementation therapy was analyzed using chi square test. All statistical tests were performed by using SPSS 15.0 version. A *P* value of < 0.05 was accepted as significant.

Results

A total of 180 potentially eligible patients were screened for study participation. Thirty-two (18%) patients were ineligible due to normal vitamin-D levels. Of 148 (82%) deficient patients, 80 were excluded (18 refused to participate and 62 did not complete follow-up). Hence, 68 CLBP patients were included in the final analysis. The average (SD) age of patients was 44 (12) with 37 (55%) being men. The mean (SD) BMI of study patients was 25.8 (3.7). Prior to inclusion into this study the participants' median (IQR) duration of CLBP was 36 (13 – 96) months and mean (SD) VAS and MODQ was found to be 81 (19) and 45 (16) showing the majority had severe pain and disability at study inclusion (Table 1).

Vitamin-D Levels

Baseline mean (SD) vitamin-D levels were found to be 12.8 (5.73) ng/mL. Sixty-one (90%) patients were

found to be vitamin-D deficient and 7 (10%) had insufficient levels. Serum vitamin-D levels increased significantly to 36.07 (12.51) post-supplementation ($P < 0.01$). Forty-five (66%) patients attained normal vitamin-D levels (> 29 ng/mL) after the vitamin-D supplementation induction phase while 18 (27%) and 5 (7%) remained insufficient and deficient, respectively (Tables 2 and 3).

Table 2. *Vitamin D status at baseline.*

	Sufficient n (%)	Insufficient n (%)	Deficient n (%)	*P* value
Baseline				
Total	-	7 (10)	61 (90)	-
Men	-	-	37 (100)	
Women	-	7 (23)	24 (77)	
After Supplementation				
Total	45 (66)	18 (27)	5 (7)	0.45
Men	26 (70)	9 (24)	2 (6)	
Women	19 (61)	9 (29)	3 (10)	

Deficient serum vitamin D levels < 20 ng/mL, Insufficient serum vitamin D levels 21 – 29 ng/mL, Sufficient serum vitamin D levels > 29 ng/mL
P value shows the comparison between men and women.

Table 3. *Vitamin D levels (n = 68).*

	Baseline	After Supplementation	*P**
Vitamin D	12.80 (5.73)	36.07 (12.51)	< 0.01

Values are presented as mean (SD) in ng/mL.
* Comparison between baseline and after treatment done by paired t-test.

Table 4. *Clinical efficacy analysis.*

Efficacy Parameter	Months	Mean (SD) (n = 68)	*P**
VAS	0	81 (19)	
	2	61 (19)	< 0.001
	3	45 (19)	< 0.001
	6	36 (18)	< 0.001
MODQ	0	45 (16)	
	2	36 (12)	< 0.001
	3	31 (13)	< 0.001
	6	26 (10)	< 0.001

Comparison made by paired t test, VAS, visual analogue scale, MODQ, modified Oswestry disability questionnaire
* Comparison are done from baseline values.

Clinical Efficacy

Significant reduction in pain score was observed post supplementation. Mean (SD) VAS scores were 61 (19), 45 (19), and 36 (18) at 2, 3, and 6 months, respectively, as compared to 81 (19) at baseline ($P \leq 0.001$ at all time intervals as compared to baseline). EPR was achieved in 36 (53%) and 43 (63.2%) patients at 3 and 6 months, respectively (Table 4, Fig. 1).

Significant improvement in functional disability was also observed post supplementation. Mean (SD) MODQ scores were 36 (12), 31 (13), and 26 (10) at 2, 3, and 6 months, respectively, as compared to baseline 45 (16) ($P < 0.001$ at all time intervals) (Table 4, Fig. 2). No adverse drug reactions were observed with oral vitamin-D supplementation in the study.

Discussion

In this open label, single arm trial we assessed the efficacy of vitamin-D supplementation in deficient patients having CLBP in terms of providing analgesia and improving functional ability. High prevalence of hypovitaminosis D 82% (148/180) was observed in the screened study patients. Results showed that two-thirds of patients achieved normalization of vitamin-D levels after supplementation. We also observed a significant reduction in pain score and improved disability with the vitamin-D supplementation at 2, 3, and 6 months, respectively.

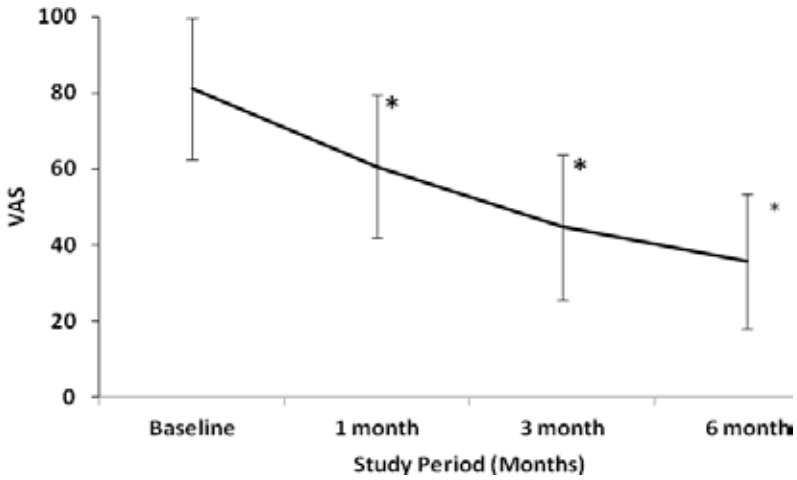
Vitamin-D plays a key role in the etiology and progression of various chronic pain conditions and associated comorbidities by exerting anatomic, hormonal, neurological, and immunological influences on pain expression (13-16). Vitamin-D deficiency induces muscle weakness and pain in adults as well as children (12,17). Vitamin D has also shown immunomodulatory actions (18). Improvement in bone density and musculoskeletal symptoms are associated with vitamin-D supplementation (19). Its supplementation could reduce the synthesis of inflammatory cytokines and increase the anti-inflammatory cytokines. Vitamin-D deficiency can affect patients of all ages and might be an underlying factor in undiagnosed musculoskeletal pain. It is a potentially treatable problem and supplementation can be an adjuvant therapy for musculoskeletal pain (20,21).

Reduced vitamin-D levels have been reported to be associated with heightened central sensitivity upon mechanical stimulation in chronic pain patients (22). It plays a profound role in astrocyte detoxification pathways, and thereby provides a neuroprotective action. The improved vitamin-D levels might be helpful in as-

trocyte detoxification pathways in the neuropathic pain component involved in CLBP patients (23). Vitamin D suppresses tumor necrosis factor alpha (TNF-α), macrophage colony-stimulating factor (M-CSF), and inducible nitric oxide synthase in astrocytes and microglia (24). TNF-α has been convincingly implicated at both peripheral and central levels of pain sensitization (25). M-CSF is a cytokine that stimulates proliferation, differentiation, and survival of monocytes and macrophages. Macrophages can release many inflammatory mediators, including proinflammatory cytokines, particularly TNF-α and interleukin-1 beta (IL-1β), nerve growth factor (NGF), nitric oxide (NO), and the prostanoids (11).

Decreased sun exposure is reported as the major cause of diminished vitamin-D synthesis (26). Holick et al (26) reported that people with naturally dark skin tone may require at least 3 to 5 times longer sun exposure to synthesize the same amount of vitamin D as people with fairer skin tone.

Obesity has also been linked with vitamin-D deficiency in both adults and children in many studies (27-30). This is due to vitamin-D stores entrapped in adipose tissue. The study patients were also found to be overweight or pre-obese, supporting the high prevalence of low vitamin-D levels in our study population. We excluded patients suffering with chronic diseases like epilepsy, psychiatric illness, and chronic inflammatory conditions as these patients must be taking anticonvulsants or corticosteroids and are likely to be at higher risk of developing vitamin-D insufficiency, as these drugs increase the catabolism of vitamin-D (26,31).

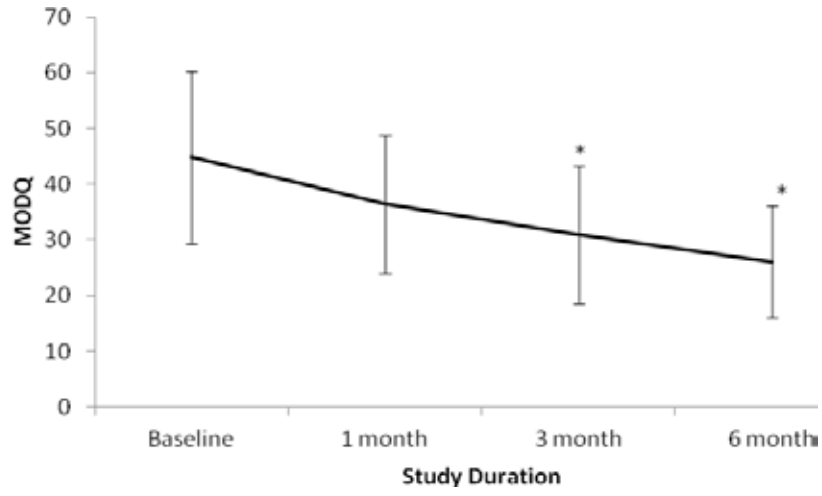


* represents significant difference when compared to baseline *P* value < 0.05

Fig. 1. *VAS during the study period.*

Vitamin-D supplementation increases plasma levels of 25(OH) D3 potentially correcting the effects of vitamin-D deficiency (32). Two recent meta-analyses conducted by Straube et al (32) have reported contrasting outcomes between the results of randomized clinical trials (RCTs) and non-RCTs. The effectiveness of vitamin-D supplementation in chronic pain treatment was observed in 10% and 95% of RCTs and non-RCTs/observational studies, respectively. The major limitation of these analyses was the fact that both meta-analyses were conducted on small and heterogeneous studies (32,33). Warner and Arnspiger (34) found no significant decrease in pain score of with ergocalciferol 200,000 IU/month administration for 3 months in patients with musculoskeletal pain. In contrast, a study conducted in non-western immigrants in Netherlands by Schreuder et al (35) has reported a small positive effect of vitamin-D supplementation in patients with nonspecific musculoskeletal pain. Further, a study conducted in a North Indian population by Kalra et al (36) has reported a high prevalence of severe vitamin-D deficiency (< 10 ng/mL) in 55.55% of cases and 10 – 30 ng/mL in 38.46% of patients with back pain. Our study participants' levels of vitamin D were also in line with Karla et al's report (36). A recently published placebo controlled trial has shown remarkable analgesic efficacy of adding 4000 IU of vitamin D in patients with musculoskeletal pain leading to faster decline in consecutive VAS scores and levels of inflammatory and pain-related cytokines (37). We did not specifically assess leg pain reduction in our study. Instead, we have used MODQ to assess the functional disability. This disability questionnaire evaluates lower limb activity particularly in terms of standing, sitting, and walking.

The recruited patients in the present study were having CLBP with or



* represents significant difference when compared to baseline *P* value < 0.05

Fig. 2. *MODQ during study period.*

without radiculopathy, were on any oral analgesic therapy, and had a stable pain score from the past 3 months. The patients receiving epidural injections for pain were excluded. However, we did not document past oral analgesic medications due to the lack of recorded details in patient files. The majority of the recruited patients did not have radiculopathy.

Our findings provide a reasonable explanation and justification for advising dietary supplementation as well as therapeutic medication to achieve normal Vitamin-D levels in patients with musculoskeletal pain. It is also important to screen vitamin-D status of at risk populations. It is advisable to get adequate sunlight exposure as well as vitamin D and calcium supplementation along with physical exercise to mitigate the morbidity induced by the disability caused by abnormal vitamin-D homeostasis.

Limitations

The results of the present study can be confounded with the effects of concomitant medications. This is a major limitation of the present as there is insufficient data regarding concomitant analgesic medications. Another major limitation is the lack of comparator as we planned this study with the observation that our regular clinic patients seem to be more deficient in vitamin D3. In addition, the regular analgesic therapy was not altered, but patients receiving epidural injections were not recruited in the study. After the induction phase, the majority reported good pain relief and the co-medications were reduced accordingly. Finally we did not document patients having radicular and axial pain specifically, which can also confound the results.

Conclusion

The present study shows that vitamin-D supplementation can improve the pain and disability in patients with CLBP. The study results should be carefully interpreted as it is a single arm, open label study and concomitant medication usage was not assessed. Altogether, intense research is needed to establish the effect of vitamin D on CLBP. RCTs with longer duration, large sample size, and different outcome assessment in different age groups are recommended.

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