

Effect of supplementation of vitamin D and calcium on patients suffering from chronic non-specific musculoskeletal pain: A pre-post study

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ABSTRACT

Background and Objective: Despite abundant sunshine, India is a country with high prevalence of vitamin D deficiency. It has been suggested that vitamin D deficiency could be a potential cause of chronic non-specific musculoskeletal pain. The study was conducted to evaluate the effect of supplementation of vitamin D and calcium on patients suffering with chronic non-specific musculoskeletal pain. **Methodology:** The experimental trial was a pre-post study conducted on 50 hypovitaminosis D patients aged 30-60 years visiting a local orthopedician or physician with complain of chronic non-specific musculoskeletal pain. Oral supplementation with vitamin D and calcium was given for 3 months. Before the intervention trial, pain, physical activity, serum vitamin D, serum calcium, body mass index and waist to hip ratio (WHR) of the respondents were assessed, which was statistically compared with post-intervention data of the same parameters. Assessment of pain was carried out using visual analog scale. Physical activity levels were compared pre and post the intervention. Also, fatigue, mood alteration, and sleep were compared. **Results:** Ninety percent of the subjects had vitamin D deficiency. Thirty-six percent of the subjects had severe chronic non-specific musculoskeletal pain, whereas 56% had moderate chronic non-specific musculoskeletal pain. The mean pain score prior to intervention was 6.22 which significantly decreased to 3.52. Mean vitamin D levels significantly rose from 17.38 ng/ml to 39.40 ng/ml. Serum vitamin D, serum calcium, and physical activity levels increased, whereas pain, weight, BMI, and WHR decreased significantly post-intervention. **Conclusions:** Supplementation with vitamin D and calcium decreases chronic non-specific musculoskeletal pain.

Keywords: Calcium, chronic non-specific musculoskeletal pain, vitamin D supplementation

Introduction

Pain is a distressing feeling which often makes the sufferer to visit a physician. It is a very common complaint. The pain could be specific to some body part or it could be diffused or vague. Pain could either arise because of some tissue injury, some underlying health condition, or it could be of unknown etiology. The pain which persists beyond the normal tissue injury and is generally

beyond 3 months and of idiopathic origin is called as chronic non-specific musculoskeletal pain (CNMP). It is defined as pain present in two regions of two contralateral limbs and in the axial skeleton.^[1] CNMP is a common complaint in pain clinics.^[2,3] CNMP substantially affects the quality of life of the sufferer. Not only the physical activities are hampered, but it takes a toll on the mental health too. Consequently, the social and economic life is affected too.^[4] Many researchers have stated that vitamin D deficiency could be possible reason of development of CNMP.^[5-17] Vitamin D thought to be a sunshine vitamin but its deficiency is prevalent even in countries with abundant sunshine such as India.^[18-20]

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Vitamin D is a hormone which is fat soluble and is part of the “calcium-vitamin D-parathyroid” hormone endocrine axis. There are two major forms of vitamin D: D₂ and D₃. When the UV-B rays from the sunrays falls on the surface of skin, vitamin D₃ is produced from the precursor-7-dehydrocholesterol. Vitamin D is first metabolized in the liver into 25-hydroxyvitamin D 25(OH)D] (vitamin D₂) and then converted to [1,25(OH)D] (vitamin D₃) in the kidneys. Vitamin D₂ is the major circulating form of vitamin D in blood and vitamin D₃ is the biologically active form. Both D₂ and D₃ are absorbed in the small intestine. Sunlight is the major facilitator of vitamin D formation in our body and it is also present in some dietary foods in small quantities. Vitamin D₃ enhances the absorption of calcium. Both vitamin D and calcium are essential in the bone and muscle metabolism.

The present study was conducted to study the effect of oral supplementation of vitamin D and calcium on pain, physical activity, weight, body mass index, waist hip ratio, and mood of patients suffering with CNMP.

Materials and Methods

This experimental trial was conducted on patients residing in city of Jaipur (Rajasthan, India), visiting a local orthopedic clinic or general physician with complain of chronic vague pains. For the same purpose, a 3-day camp was organized inviting patients suffering with persistent pain of unknown cause. The patients were screened for CNMP with the help of an orthopedic surgeon. Based on the exclusion and inclusion criteria of the study [Table 1] and their willingness to participate in the study, patients were recruited for the intervention trial of 3 months. The respondents were explained about the study objectives and the expected results. Written consent was obtained from all the participants of the study.

Before the intervention trial, pain, physical activity, serum vitamin D, serum calcium, BMI (Body Mass Index), and WHR (Waist to Hip ratio) of the respondents were assessed. Weight was recorded using digital weighing scale to the nearest 100 g. Height was recorded using a stadiometer to nearest 0.1 cm and the waist and hip circumferences were recorded using a non-stretchable measuring tape to nearest 0.1 cm. WHO cutoffs for Asian-Indians were used to interpret results of BMI and WHR.^[21]

Pain was assessed using a visual analog scale (VAS), under the supervision of a physician. The VAS ranged from score 0 (no pain) to score 10 (worst pain), with 0.2| 4.6, and 8.10 being categorized as low, moderate, and severe pain, respectively. Two day physical activity recall of the respondents was recorded and the average of the two day PAL (physical activity level) values were calculated.

Serum vitamin D and serum calcium levels were estimated using chemiluminescence method.^[22] Vitamin D levels 0–19 ng/ml,

Table 1: Inclusion and exclusion criteria of the study

Inclusion criteria	Exclusion criteria
Residents of Jaipur City	Pregnancy
Age 30-60 years	Elderly (>60 years)
CNMP >3 months	Use of vitamin D or calcium supplements in last 4 months
Patients with serum haemoglobin ≥ 9 g/dl	Patients suffering from anaemia (haemoglobin <9 g/dl). Patients suffering from any underlying disorder that can cause pain

20–30 ng/ml, and 31 ng/ml and more were considered deficient, insufficient, and sufficient, respectively.^[23] The optimal range for serum calcium was considered 8.5–10.5 mg/dl.^[24] Choosing the most appropriate method for vitamin D measurement depends on where it needs to be applied, degree of specificity required and financial aspects.^[25]

In the intervention trial of 3 months, the respondents were given an oral therapeutic dose of 60,000 IU of vitamin D orally once weekly for 1 month, and then 60,000 IU once a month for next 2 months. Calcium supplement of 1,000 mg was given twice a day in two divided doses of 500 mg each, every day for 3 months. To check for the compliance, patients were asked to show empty sachets and wrappers on each follow-up. The patients were also followed up telephonically. One researcher also studied a similar dosage pattern.^[26]

At the end of the trial, pain, physical activity, serum vitamin D, and serum calcium levels of the subjects were measured again. The respondents' weight, waist circumference, and hip circumference were recorded and the post-test BMI and WHR calculated. Patients were asked to report if they suffered with fatigue before and after the treatment. They were also asked to report any mood alterations or sleep disturbances. Pre-test values of all the parameters were compared with the post-test values and analyzed statistically.

Statistical analysis

Data were analyzed by the Statistical Package for the Social Sciences (SPSS) version 16.0, software for Windows (SPSS, Chicago, Illinois, USA). Mean, standard deviations and percentages were calculated for univariate parameters. Chi-square test and Spearman's rho correlation coefficient were performed where appropriate.

Ethical approval and Patient consent

Ethical approval for conducting the research was obtained from by Departmental Ethical Committee, Department of Home Science, University of Rajasthan, Jaipur. Written consent was obtained from the respondents who participated in the study. Approval from the ethical committee has been obtained from The Departmental Ethical Committee, Department of Home Science, University of Rajasthan, Jaipur. A copy of the same has been uploaded on the journal's site. The approval was obtained on November 14, 2014.

Results

A total of 3,000 patients were screened for CNMP and 370 (12.33%) were found to be suffering with CNMP. Among these 370, 65 respondents took part in the intervention study. Excluding the dropouts among these, 50 patients completed the intervention study. Fifteen patients did not complete the full protocol because they did not attend the subsequent interviews. Analysis of outcome at the end of three months was based on 50 subjects.

Out of 50 respondents, 34 were females and rest males. Serum vitamin D was found deficient in 68% of the patients. Twenty-two percent had insufficient and 10% had sufficient serum vitamin D levels. Serum calcium levels was found appropriate in 68% of the respondents, whereas 22% had low levels. Thirty six percent of subjects had severe pain, whereas 56% had moderate non-specific musculoskeletal pain. As evident in Table 2, post the intervention trial, serum levels of vitamin D and calcium rose significantly.

There was an increase in the physical activity levels of the patients. The mean pain score significantly decreased from 6.22 to 3.52 because of intervention. Mean vitamin D levels significantly rose from 17.38 ng/ml to 39.40 ng/ml. A non-significant decrease in BMI was observed at the post-intervention stage. Seventy one percent of women and

94% of men had undesirable WHR which decreased to 62% and 80%, respectively.

Among all the grades of pain, a significant increase in serum vitamin D levels after three months of intervention was observed [Table 3]. There was an increase in serum calcium levels in patients suffering from moderate and severe pain while those with low pain did not show any change [Table 4].

A correlation between serum vitamin D, serum calcium, pain, and PAL has been given in Table 5.

Prior to the treatment, 64% of the patients reported fatigue which decreased to 34% after the treatment. Before the intervention, 74% of respondents reported a decrease in sleep which could be because of the pain, which decreased to 20% after the supplementation. More than half of the patients (52%) reported an improvement in their sleep disturbances with relief in pain. Prior to the intervention, 36 respondents (72%) reported various kind of mood disturbances such as anger, irritability, stress, low confidence, poor concentration, memory loss of crying. After the supplementation, 48 out of the 50 respondents reported an improvement in the mood disturbances after the intervention. The rest two patients who reported normal mood were the ones who had reported no mood alteration prior to the intervention because of pain.

Table 2: Effect of supplementation of vitamin D and calcium on various parameters

Variables (unit)	Mean of various variables		t (P)
	Pre intervention Stage	Post intervention Stage	
Serum vitamin D (ng/ml)	17.38±7.61	39.40±10.69	-21.581 (0.000)**
Serum calcium (mg/dl)	9.45±0.96	9.73±0.56	-3.279 (0.002)**
PAL	1.56±0.24	1.71±0.25	-12.988 (0.000)**
Pain score	6.22±2.06	3.52±1.54	13.466 (0.000)**
Weight (kg)	66.53±11.61	65.01±10.90	5.632 (0.000)**
BMI (kg/m ²)	26.17±4.65	25.57±4.34	5.436 (0.000)**
WHR	0.90±0.06	0.89±0.036	4.184 (0.000)**

*Significant at 95% level of significance; **Significant at 99% level of significance; figures in parenthesis are P values

Table 3: Serum vitamin D levels at pre and post intervention stage amongst patients suffering from different grades of pain

Pain category	Pain score	Mean serum vitamin D level (ng/ml)		t (P)
		Pre intervention Stage	Post intervention Stage	
Low (n=4)	≤2	20.82±7.89	47.68±10.23	12.823 (0.001)**
Moderate (n=29)	4-6	17.66±7.31	40.76±10.79	16.455 (0.000)**
Severe (n=17)	8-10	16.08±8.19	35.12±9.31	12.618 (0.000)**

*Significant at 95% level of significance; **Significant at 99% level of significance; figures in parenthesis are P

Table 4: Serum calcium levels at pre and post intervention stage amongst patients suffering from different grades of pain

Pain category	Pain score	Mean serum calcium level (mg/dl)		t (P)
		Pre intervention Stage	Post intervention Stage	
Low (n=4)	≤2	9.69±1.22	9.90±0.60	0.626 (0.575)NS
Moderate (n=29)	4,6	9.49±0.99	9.72±0.64	2.114 (0.044)*
Severe (n=17)	8,10	9.32±0.87	9.72±0.40	2.431 (0.027)*

NS: Non-Significant; *Significant at 95% level of significance; **Significant at 99% level of significance; figures in parenthesis are P

Table 5: Correlation between serum vitamin D, serum calcium, pain, and PAL

Parameters	Serum vitamin D	Pain score	Serum calcium	PAL
Serum vitamin D	1.000 (-)	-0.594** (.000)	0.370** (.000)	0.291** (.003)
Pain score	-0.594** (.000)	1.000 (-)	-0.150 (.136)	-0.284** (.004)
Serum calcium	0.370** (.000)	-0.150 (.136)	1.000 (-)	0.196 (.050)
PAL	0.291** (.003)	-0.284** (.004)	0.196 (.050)	1.000 (-)

**Correlation is significant at the 0.01 level (2-tailed); figures in parenthesis are *P* values

Discussion

Due to the realization of prevalence of high deficiency of vitamin D, many researchers have studied the vitamin, and a lot of skeletal and extra-skeletal symptoms of deficiency have been identified.^[27-29]

In our study, incidence of CNMP was found to be 12.33%. In a study, it was shown that patients with persistent, nonspecific musculoskeletal pain were at high risk of vitamin D deficiency which often goes misdiagnosed. It was estimated that among patients suffering with chronic pain, only a quarter of patients suffer with pain at a specific origin, others suffer with pain of unknown origin and unidentified etiology.^[16] Pain associated with vitamin D deficiency has a special characteristic that it is usually sensed on the bone or the muscle.^[30] Authors have suggested that vitamin D deficiency could be an origin of non-specific musculoskeletal pain including low back pain.^[8,31]

When the mean serum levels of vitamin D of patients with non-specific pain were compared with the control group, it was observed that there was a positive relation between vitamin D deficiency and skeletal pain. This association was greater in women than men. A similar study proved the same.^[32] In patients with chronic back pain, mean level of serum vitamin D assessed was 18.4 ng/mL (19.6 ng/ml for women, 17.3 ng/ml for men), which was insufficient.^[33] In a study conducted on adult OPD patients suffering with non-specific complaints of general body pain, back pain, tiredness, and weakness, it was revealed that 40.2% male and 37% females were deficient in vitamin D.^[34]

There are several mechanisms to show that vitamin D deficiency could be involved in causing pain. Vitamin D deficiency can cause loss of anti-inflammatory, anti-apoptotic, or anti-fibrotic effects.^[35] Vitamin D is mediated by vitamin D receptors which are present on skeletal muscle cells, thus proving its function there.^[36] Vitamin D causes increased activity of bone deforming cells (osteoclasts) and decreases activity of bone forming cells (osteoblasts) and results in low bone mineralization producing bone pain.^[37] Vitamin D deficiency enhances sensitivity to pain due to stimulation of nerve cells.^[38] It suppresses proinflammatory cytokines such as Tumor necrosis factor alpha and Macrophage colony-stimulating factor.^[39] Vitamin D upregulates the synthesis of neurotrophins such as nerve growth factor, neurotrophin 3, and glial cell line-derived neurotrophic factor, whereas it downregulates neurotrophin-4.^[40]

Vitamin D could be involved in metabolism of muscles and nerves. It was found in our study that supplementation therapy caused a significant increase in the serum levels of calcium and vitamin D and a significant reduction in pain scores. Pain score was negatively associated with serum levels of vitamin D. There was a highly significant rise in the physical activity levels after the intervention. The shift in PAL could be attributed to the relief in pain which initially might be causing hindrance in performing physical activities. There was also an evidence of improvement in mood disorders of the patients after the intervention. Thus, vitamin D could also have an anti-depressive effect.^[41] Intervention trial brought about a highly significant fall in weight, BMI, and WHR. There was a decrease in the number of respondents with morbid obesity. The decrease in BMI could be attributed to increase in ability or willingness to perform physical activity.

In a study conducted on 28 US veterans suffering with chronic pain it was revealed that all of them reported difficulty in sleep and that when these patients were supplemented with vitamin D for 3 months, there was improvement in efficacy of sleep.^[42] Other authors have also reported that there is betterment in sleep, mood, wellbeing, and various aspects of quality of life with vitamin D supplementation.^[43,44]

Vitamin D supplementation in suitable doses must be encouraged in those who are deficient and the “at-risk” population. Vitamin D supplementation must be accompanied with appropriate age-related calcium intake.^[45] Vitamin D supplementation in individuals with a normal serum vitamin D could have an impact of limited duration, but could be of greater benefits to individuals with low levels of serum vitamin D.^[46] Vitamin D supplementation could be beneficial in the treatment regime of primary care physicians. Many patients visit general practitioners for various kinds of pain. Findings of this study could help physicians treat patients with persistent vague pains. Physicians may discuss the possibility of vitamin D deficiency in patients suffering from chronic nonspecific musculoskeletal pain.

There are such diverse functions of vitamin D that it could be potentially beneficial in pharmaceutical applications.^[47] Serum variations in the vitamin D status of the individuals could arise because of genetic differences in the vitamin D related enzymes. It could also be varied because of the underlying conditions of the patients especially those suffering with chronic pains. Also, there is difference in perception of pain person to person. To determine the pain-relaxing effect of vitamin D, it is important to consider the variations in the expression and assessment of

pain by the patients^[48] Vitamin D clearly cannot be a solution to cure various skeletal and extra skeletal diseases, but could be a feasible, economical, and a safe accessory-therapy for some disease conditions.^[49]

It could be said that more women than men were found to be suffering with CNMP. A huge number of individuals do not have a sufficient vitamin D status and many of them suffer with CNMP. Supplementation with vitamin D and calcium to vitamin D deficient patients suffering with CNMP might bring about a considerable relief in the painful conditions. It may also enhance the physical activity capacity. Relieving the painful conditions improves the physical, mental, and social wellbeing of the individual.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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