Original Article

A prospective, cross-sectional study on association of serum vitamin D level with musculoskeletal symptoms and blood pressure in adult population

Vikram Singh[1], Arup Kumar Misra[2], Mridu Singh[1], Bharat Kumar[3], Naresh Kumar Midha[3], Sneha Ambwani[4]

[1]Department of Medicine, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, [2]Department of Pharmacology, All India Institute of Medical Sciences (AIIMS), Mangalagiri, Andhra Pradesh, [3]Departments of Medicine and [4]Pharmacology, All India Institute of Medical Sciences (AIIMS), Jodhpur, Rajasthan, India

Abstract

Background: Vitamin D is an important vitamin required to maintain an important physiological function of the body. The body should maintain an optimal level of vitamin D to maintain skeletal and metabolic functions. It was observed that inverse relationship is maintained by vitamin D level in the body with musculoskeletal symptoms and metabolic disorders. **Objective:** The study is conducted to associate between serum levels of vitamin D with self-reported symptoms (musculoskeletal) and blood pressure. **Material and Methods:** Venous blood sample was collected from 126 adults with musculoskeletal symptoms. The subjects were stratified based on their vitamin D levels. Groups were tested for the frequency of symptoms and the relationship of different parameters with vitamin D. **Results:** The frequency of subjects in the study was more in the deficient category (<20 ng/dL). In the study, vitamin D was found to have a significant association with "weakness." Body mass index (BMI), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were found to have an inverse relation with serum vitamin D level. **Conclusion:** The study showed the effect of vitamin D level in musculoskeletal symptoms and inverse association of vitamin D with BMI and blood pressure.

Keywords: Blood pressure, body mass index, hypovitaminosis, musculoskeletal symptoms, vitamin D

Introduction

Vitamin D deficiency is prevalent worldwide and it is estimated that about one billion people may have low vitamin D levels across all ethnicities and age groups.[1] Vitamin D is essential for the growth and maintenance of bone and skeletal tissues. Vitamin D3 (cholecalciferol) is produced naturally from skin exposure to sunlight and small amounts of it come from dietary sources. One of the important reasons for this global pandemic is the lack of exposure to the sun and very few foods naturally contain vitamin D (wild-caught salmon and UV-exposed mushrooms).[2] Vitamin D has multiple roles in body functions which include cellular regulation, muscle function, calcium absorption, bone metabolism, and immune function.[3]

Vitamin D deficiency has been found to be associated with other disorders namely secondary hyperparathyroidism, hypertension, diabetes mellitus, inflammatory bowel disease, cardiovascular disease, stroke, osteoporosis and osteoporotic fractures, mental illness, chronic pain, cancers, etc.[4] Vitamin D deficiency causes hypocalcemia, bone loss, and muscle weakness manifested by musculoskeletal pain.[5,6]

Address for correspondence: Dr. Arup Kumar Misra, Department of Pharmacology, All India Institute of Medical Sciences, Mangalagiri, Andhra Pradesh, India.
E-mail: arup2003m@gmail.com

Received: 10-10-2019 **Revised:** 12-02-2020
Accepted: 14-02-2020 **Published:** 26-03-2020

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_872_19

How to cite this article: Singh V, Misra AK, Singh M, Kumar B, Midha NK, Ambwani S. A prospective, cross-sectional study on association of serum vitamin D level with musculoskeletal symptoms and blood pressure in adult population. J Family Med Prim Care 2020;9:1628-32.

A number of scientific evidence supports the multidimensional consequences of Vitamin D deficiency on health.[5,6] Though, there is a lack of consensus regarding optimum vitamin D serum level, it is defined when the circulating levels of 25-hydroxyvitamin D {25(OH)D} is less than 20 ng/mL.[7] Hence, appropriate evaluation of its serum level and its effect on the organ system will help to select the treatment modalities in terms of dose, dosing interval, and formulation of vitamin D supplementation to maintain the adequate vitamin D level.[8] Recent studies in India have shown increase prevalence of vitamin D deficiency in urban and rural populations. This requires a large number of specialists, primary care physicians, and family physicians to cater to this burden on the society.

Thus, we planned this study to assess the prevalence and its effects on lifestyle and quality of life on the people of northwest India.

Material and Methods

An observational and cross-sectional study conducted in the department of general medicine at a tertiary care teaching hospital. The duration of the study was 3 months. Adults (18–65 years of age) attending the out-patients department of general medicine were included in the study based on the following criteria:

Inclusion criteria:

1. Patients between 18 and 60 years, of either gender with musculoskeletal symptoms suggestive of vitamin D deficiency.

Exclusion criteria:

1. Pregnant and lactating women
2. Patients above 60 years
3. A patient who has taken vitamin D in the last 3 months
4. A patient suffering from thyroid disorders, parathyroid disorders, renal disorders, and metabolic disease
5. Patients on steroids and other factors influencing vitamin D.

Sample Size: 126 patients (age between 18 and 60 years) with musculoskeletal features suggestive of vitamin D deficiency were randomly selected for the study duration of 3 months.

Ethical consideration

Ethical clearance was taken from the institutional ethical committee with Ethical Clearance Certificate No. AIIMS/IEC/2017/759 (27/01/2017).

Sociodemographic clinical profile data

A structured pro forma was used to record a certain demographic. Body mass index (BMI) was calculated as weight (kilograms) divided by the square of height (meters). On the basis of BMI, the subjects were divided into obese (≥25 BMI), overweight (≥23 BMI but <25 BMI), and normal (<23 BMI) based on the revised consensus guidelines for India.[9]

A clinical profile sheet was designed for the study to record various clinical parameters like age of onset, duration of illness; time spent in episodes/illness exacerbations, clinical features suggesting of musculoskeletal origin, and venous blood samples were collected to measure the level of vitamin D level. As the patients were mostly from a rural area and uneducated, pain analog scale was not used rather all of the responses to the symptoms were categorized into binary scales as yes for symptomatic and no for asymptomatic.[10]

Procedure of estimation of vitamin D

25-hydroxy vitamin D estimation was done by chemiluminescence immunoassay (CLIA), a quantitative immunoassay method processed by a fully automated analyzer, (DiaSorin LIAISON, Germany), available in the department of biochemistry of the hospital.

The cutoff to define an inefficient/insufficient when circulating concentration of 25(OH) D is above 20 ng/dL but less than equal to 29 ng/dL, while concentrations lower than 20 ng/dL are categorized as deficient. Subjects who were having serum vitamin D level was ≥30 ng/dL are classified as not deficient (ND) or normal.[11]

Statistical analysis

Data were compiled using Microsoft Excel and analyzed using SPSS software (IBM-SPSS statistics 21.0; SPSS Inc., Chicago, IL, USA). Quantitative variables were expressed as mean ± standard deviation (Mean ± SD) and numbers (percentages). Normality distribution of data was first determined by the Kolmogorov–Smirnov test. As data were found to be normally distributed, the parametric analysis was used throughout the analysis. Pearson correlation was used to study the correlation between vitamin D and numerical variables. A Chi-square test was used for categorical variables. *P* values less than 0.05 were considered statistically significant for all tests.

Results

In the study, Table 1 presents the demographic data of all patients present with musculoskeletal symptoms. The subjects with self-reported symptoms were stratified according to vitamin D levels into three groups: subjects in the deficient category with vitamin D less than 20 ng/dL, subjects in the insufficient category with vitamin D between 20 and 29 ng/dL, and normal category with vitamin D above and equal to 30 ng/dL. It was found that most of the subjects belong to the category of deficient (76.8%). No significant association was found between age and sex with vitamin D in the study. In the demographic data, it was found that sun exposure had significant effects on the vitamin D level of the subjects ($P = 0.040$) [Table 1]. Demographic data showed that vitamin D also has a significant effect on the weight and BMI ($P < 0.05$) in the total population of the sample. It also had a significant effect on diastolic blood pressure (DBP) ($P < 0.05$) [Table 1]. In the demographic data,

Table 1: Demographic characteristics of subjects with self-reported symptoms and correlation with Vitamin D

Demographic characteristics	Patients (*n*=126)	Pearson correlation	*P* (two-sided)
Age (years)†	37.84±10.21	0.127	0.157
Gender-			
Male†† (‡‡)	42 (33.6)		
Female†† (‡‡)	83 (66.4)		
Diet-Vegetarian†† (‡‡)	97 (76.98)		
Nonvegetarian†† (‡‡)	28 (22.22)		
Weakness†† (‡‡)	75 (60)		
Bone pain†† (‡‡)	60 (48)		
Body ache†† (‡‡)	68 (54.4)		
Lethargy†† (‡‡)	22 (17.6)		
Fatigue†† (‡‡)	6 (4.8)		
Numbness†† (‡‡)	5 (4)		
Sun exposure (Hours)†	1.24±1.69	0.184*	0.040
Weight†	65.33±16.31	−0.270*	0.002
Height†	163.36±9.07	−0.137	0.129
BMI†	24.42±5.60	−0.231*	0.009
SBP†	120.25±14.25	−0.151	0.094
DBP†	79.26±9.11	−0.181*	0.043

††number, ‡‡percentage, †mean±SD, *P*<0.05 is considered significant, *Correlation significant at 0.05 level. BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure and ng/dL=Nanogram per deciliter

a number of the subject with "weakness" was found more than the other symptoms [Table 1].

In Table 2, the subjects with musculoskeletal symptoms were stratified according to the deficient, insufficient, and normal category of vitamin D level. Descriptive data showed that the number of musculoskeletal symptoms was more in the deficiency category. Weakness (52.8%), bone pain (38.4%), body ache (38.4%), lethargy (13.6%), fatigue (4%), and numbness (4%) were found more in the subjects whose vitamin D level is less than 20 ng/dL. As vitamin D levels improve, the number of symptoms also decreased drastically. No significant associations were also found between symptoms (bone pain, body ache, fatigue, lethargy, and numbness) and vitamin D in the study. Though the impact of vitamin D on musculoskeletal symptoms might not be that significant due to the small sample size but the symptoms due to the vitamin D deficiency are inversely proportional to its level in the body.

The subjects who have less than 20 ng/dL of vitamin D were found to have a statistically significant correlation with exposure to sunlight ($P = 0.001$). As the duration of exposure to sunlight increases, the level of vitamin D also improves [Table 3]. On the other hand, subjects with deficient vitamin D levels had consistently higher values of BMI, systolic blood pressure (SBP), and DBP [Table 3]. Although vitamin D does not have statistical significance result in these parameters in the deficient, insufficient, and normal category, the descriptive data indicate that vitamin D has an inverse relation with these parameters.

Discussion

Vitamin D is a secosteroid hormone that is essential for skeletal health and the health of non-skeletal tissue such as cardiovascular, endocrine, metabolic, neurological, neoplastic, articular, immunological, etc. Its deficiency is endemic and has been associated with numerous diseases.

Skin is the principal organ for the production of vitamin D in the body. It is produced at an extraordinary speed after a short exposure to sunlight, the quantity produced is more than the dietary sources.[12,13] It was found that fair-skinned people produced more vitamin D (20,000 IU) after 30 min of exposure to sunlight which is comparable to drinking 200 glasses of milk (100 IU/8 oz. glass) or taking 50 standard multivitamins (400 IU/tablet) to obtain the same amount.[14] In fact, many studies were done in India shown the widespread prevalence of hypovitaminosis D and osteomalacia.[15] Many studies have a different opinion regarding the relationship between vitamin D level and its effect on the independent parameters which might vary in our results.[16] Our study showed that there was a positive relationship between the duration of exposure to sunlight and vitamin D level. It was found that almost 76% of subjects are in the deficient vitamin D (0–20 ng/dL) category due to less exposure to sunlight. Maybe because of two reasons: First, study was conducted in the semiarid region (extreme climate) of the country with increasing urbanization,[17] where-in people are found to be staying indoors, wearing excessive clothing to protect from sunlight, mostly dark-skinned and some were consciously avoiding the sun, thus, landing them into deficiency of vitamin D. Second, more than two-thirds of our study population was vegetarian and was found having less than 30 ng/dL of vitamin D level. As vegetarian population usually has minimal vitamin D in the diet.

The present study finds significant correlations among vitamin D and weakness, one of the most self-reported symptoms which constitute 60% of the symptoms in the overall population. We found that subjects with deficient levels of vitamin D had

Table 2: Stratification of patients according to vitamin D level and its relationship with musculoskeletal symptoms

Vitamin D (ng/dL)	<20	20-29	≥30
No. of patients†† (‡‡)	96 (76.8)	18 (14.4)	11 (8.8)
Weakness†† (*)	66 (0.540)	6 (0.114)	3 (0.237)
Bone pain†† (*)	48 (0.424)	6 (0.888)	6 (0.244)
Body ache†† (*)	48 (0.106)	14 (0.150)	6 (0.417)
Lethargy†† (*)	17 (0.630)	4 (0.270)	1 (0.735)
Fatigue†† (*)	5 (0.177)	1 (0.434)	ND
Numbness†† (*)	5 (0.960)	ND	ND

††number, ‡‡percentage, *P<0.05 is considered significant, ND: No data

Table 3: Stratification of patients according to vitamin D level and its relationship with sun exposure, BMI, SBP, and DBP

Vitamin D (ng/dL)	<20	20-29	≥30
No. of patients†† (‡‡)	96 (76.8)	18 (14.4)	11 (8.8)
Sun exposure (Hours) (¶)/*	1.14±1.63 (0.001)	1.44±1.64 (0.529)	1.81±2.10 (0.338)
BMI (¶)/*	25.01±5.50 (0.222)	23.11±5.67 (0.809)	21.4±4.96 (0.599)
SBP (¶)/*	121.70±15.1 (0.881)	115.11±9.29 (0.429)	116±9.83 (0.745)
DBP (¶)/*	80.12±9.56 (0.455)	76.67±5.65 (0.986)	76±8 (0.641)

††number, ‡percentage, ¶mean±SD=Mean plus minus standard deviation, *P<0.05 is considered significant

the maximum complaint compared to subjects with insufficient and normal levels. Muscular weakness, chronic musculoskeletal pain, easy fatigue or lethargy are extremely common symptoms of vitamin D deficiency.[18] As deficiency of vitamin D causes decreased absorption of calcium leading to bone demineralization; further its receptors in muscles are unstimulated leading to skeletal fragility and aggravate the musculoskeletal symptoms of muscle weakness, bone pain, the lethargy that increases the risk of falls, osteomalacia, and osteoporosis.[19]

Although our findings are similar to other studies,[20] few studies do not support such association[16] which is due to different criteria of inclusion, duration of symptoms, lack of control group, seasonal variation, ethnic homogeneity of populations, and many others.

BMI showed a significant relationship with vitamin D levels in many studies. Low vitamin D level is associated with excess adiposity, due to the sequestration of the fat-soluble vitamin within the adipose tissue or the effect of volume dilution because of the larger body size.[21] The relationship between vitamin D and obesity is controversial and unclear. There are several hypotheses and mechanisms proposed between the associations of vitamin D and obesity. On one hand, it's proposed that vitamin D deficiency was a consequence of obesity and on the other hand, it was a predisposing factor to obesity. One study found that supplementation of vitamin D3 in healthy overweight and obese women decrease body fat mass with increasing 25(OH)D concentrations.[22] Another study found that vitamin D deposition in body fat also decreases the serum level of vitamin D3.[23]

The present study finds significant correlations among vitamin D and BMI in the total subjects which are clinically as well as statistically significant as compared with established studies.[22-24] The correlation between vitamin D level and BMI may because of following reason: First, people with overweight or obesity (higher BMI) are less exposed to sunlight which is true in our study; Second, people with high BMI have dietary intake which is deficient of vitamin D; third, among obese patients, there is reduced bioavailability of vitamin D and lastly vitamin D gets sequestered in adipose tissue thus lowering its serum levels in obese patients.[24]

The present study finds significant correlations between vitamin D levels and blood pressure in the total population. The study shows an inverse relationship between SBP, DBP, and vitamin D level. A recently published meta-analysis (14 cross-sectional studies, 4 prospective studies) showed that the pooled odds ratio of hypertension was significant enough and concluded that calcitriol level is having an inverse relationship with hypertension.[21,25] The mechanism proposed for the inverse relationship between vitamin D and hypertension is as follows. First, calcitriol inhibits renin synthesis in the kidney; second, high parathyroid hormone levels to secondary hyperparathyroidism in vitamin D deficiency state affects vascular smooth muscle cells and increases vascular stiffness; and last, vitamin D deficiency is also associated with endothelial dysfunction and could promote increased atherosclerosis and systolic hypertension.[26] However, statistically, it was found that the values are significant for DBP than SBP which is contrary to a small trial by Pfeiffer *et al.*[27]

Conclusion

The study showed that the subjects with symptoms of weakness were more in the deficient level (<20 ng/dL). It was also found that sun exposure had a significant effect on the vitamin D level in the total subjects but more for those who are having vitamin D levels less than 20 ng/dL. There was a significant correlation between vitamin D on the BMI of the total subject in the study. The study shows an inverse relationship between SBP, DBP, and vitamin D level.

We realize that this study has a few limitations. We focused on vitamin D levels of the adult population who were relatively healthy so it would be of great interest to do similar studies on patients with chronic diseases. Further, since it is a pilot study, so the sample size was not large. It was also highlighted that there was an association between vitamin D levels and dependent symptoms in the deficient category even though the impact is not significant. Thus, to improve the impact, a larger population may be required. Further studies are needed to shed more light on their possible association in relation to symptoms in health and disease. This study might help the primary care physicians, family physicians, and specialist doctors to maintain the standards of care for the population by following the latest, evidence-based practice.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Palacios C, Gonzalez L. Is vitamin D deficiency a major global public health problem? J Steroid Biochem Mol Biol 2014;144PA:138-45.
2. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266-8.
3. Pfeifer M, Begerow B, Minne HW. Vitamin D and muscle function. Osteoporos Int 2002;13:187-94.
4. Hofstede H, van der Burg HA, Mulder BC, Bohnen AM, Bindels PJ, de Wit NJ, *et al.* Reducing unnecessary vitamin testing in general practice: Barriers and facilitators according to general practitioners and patients. BMJ Open 2019;9:e029760.
5. Singh V, Misra AK, Singh M, Midha NK, Kumar B, Ambwani S, *et al.* An open-label, randomized, 10 weeks prospective study on the efficacy of vitamin D (daily low dose and weekly high dose) in vitamin D deficient patients. J Family Med Prim Care 2019;8:1958-63.
6. Tedeschi SK, Aranow C, Kamen DL, LeBoff M, Diamond B, Costenbader KH. Effect of vitamin D on serum markers of bone turnover in SLE in a randomised controlled trial. Lupus Sci Med 2019;6:e000352.
7. Pepper KJ, Judd SE, Nanes MS, Tangpricha V. Evaluation of vitamin D repletion regimens to correct the vitamin D status in adults. Endocr Pract 2009;15:1595-603.
8. Holick MF. The vitamin D deficiency pandemic and consequences for nonskeletal health: Mechanisms of action. Mol Aspects Med 2008;29:361-8.
9. Aziz N, Kallur SD, Nirmalan PK. Implications of the revised consensus body mass indices for Asian Indians on clinical obstetric practice. J Clin Diagn Res 2014;8:OC01-3.
10. Azizieh FA, Alyahya KO, Dingle K. Association of self-reported symptoms with serum levels of vitamin D and multivariate cytokine profile in healthy women. J Inflamm Res 2017;10:19-28.
11. Pramyothin P, Holick MF. Vitamin D supplementation: Guidelines and evidence for subclinical deficiency. Curr Opin Gastroenterol 2012;28:139-50.
12. Zhang X, Liu Z, Xia L, Gao J, Xu F, Chen H, *et. al.* Clinical features of vitamin D deficiency in children: A retrospective analysis. J Steroid Biochem Mol Biol 2019:105491.
13. Hochberg Z, Hochberg I. Evolutionary perspective in rickets and vitamin D. Front Endocrinol (Lausanne) 2019;10:306.
14. Hollis BW. Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: Implications for establishing a new effective dietary intake recommendation for vitamin D. J Nutr 2005;135:317-22.
15. Arya V, Bhambri R, Godbole MM, Mithal A. Vitamin D status and its relationship with bone mineral density in healthy Asian Indians. Osteoporos Int 2004;15:56-61.
16. McBeth J, Pye SR, O'Neill TW, Macfarlane GJ, Tajar A, Bartfai G, *et al.* Musculoskeletal pain is associated with very low levels of vitamin D in men: Results from the European Male Ageing Study. Ann Rheum Dis 2010;69:1448-52.
17. Agarwal KS, Mughal MZ, Upadhyay P, Berry JL, Mawer EB, Puliyel JM. The impact of atmospheric pollution on vitamin D status of infants and toddlers in Delhi, India. Arch Dis Child 2002;87:111-3.
18. Erkal MZ, Wilde J, Bilgin Y, Akinci A, Demir E, Bodeker RH, *et al.* High prevalence of vitamin D deficiency, secondary hyperparathyroidism and generalized bone pain in Turkish immigrants in Germany: Identification of risk factors. Osteoporos Int 2006;17:1133-40.
19. Bischoff HA, Borchers M, Gudat F, Duermueller U, Theiler R, Stahelin HB, *et al. In situ* detection of 1,25-dihydroxyvitamin D3 receptor in human skeletal muscle tissue. Histochem J 2001;33:19-24.
20. 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. Clin J Pain 2013;29:341-7.
21. Heller JE, Thomas JJ, Hollis BW, Larson-Meyer DE. Relation between vitamin D status and body composition in collegiate athletes. Int J Sport Nutr Exerc Metab 2015;25:128-35.
22. Vashi PG, Lammersfeld CA, Braun DP, Gupta D. Serum 25-hydroxyvitamin D is inversely associated with body mass index in cancer. Nutr J 2011;10:51.
23. Burgaz A, Orsini N, Larsson S C, Wolk A. Blood 25-hydroxyvitamin D concentration and hypertension: A meta analysis. J Hypertension 2011;29:636-45.
24. Minambres I, Sanchez-Hernandez J, Sanchez-Quesada JL, Rodriguez J, de Leiva A, Perez A. The association of hypovitaminosis D with the metabolic syndrome is independent of the degree of obesity. ISRN Endocrinol 2012;2012:691803.
25. Bhandari SK, Pashayan S, Liu Ila, Rasgon SA, Kujubu DA, Tom TY, *et al.* 25-hydroxyvitamin d levels and hypertension rates. J Clin Hypertens 2011;13:170-7.
26. Li CJ, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 1,2-dihydroxyvitamin D3 is a negative endocrine regulator of the renin-angiotensin system. J Clin Invest 2002;110:229-38.
27. Vimaleswaran KS, Cavadino A, Berry DJ; LifeLines Cohort Study investigators, Jorde R, Dieffenbach AK, *et al.* Association of vitamin D status with arterial blood pressure and hypertension risk: A Mendelian randomisation study. Lancet Diabetes Endocrinol 2014;2:719-29.