Original article High prevalence of hypo-vitaminosis D among patients presenting with chronic diffuse Musculo-skeletal pain at a tertiary care hospital in-sub-Himalayan region of India

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Abstract
Problem: Hypovitaminosis D is thought to be rarity in India country because of abundant sunshine. It is an important differential diagnosis for patients presenting with musculoskeletal pains. We conducted this study to estimate the prevalence of hypovitaminosis-D in one sub-set of population i.e. patients presenting with diffuse muscular-skeletal pains. **Approach:** All adult (≥18 years) patients presenting to the out-patient department of general medicine, Indira Gandhi Medical College & Hospital (IGMC), Shimla, from May 1, 2008 through April 30, 2011 with diffuse musculoskeletal pain were included. Detailed history, clinical examination and biochemical investigation including vitamin D levels were done. Serum 25(OH) D was measured by radioimmunoassay (RIA). Patient with vitamin D deficiency status were treated with oral cholecalciferol and later followed up. Statistical analysis was done using EpiInfo Software version 3.5.3 for windows. **Findings:** We surveyed 296 patients and 231 (78.0%) of these were women. Age of the participants ranged from 19-78 years with a mean of 45.6±13.9 yearsParticipants from rural areas were 218 (73.6%).The levels of 25(OH) D ranged from1.7 ng/mL to 64.4 ng/mL. Mean 25(OH) D level (ng/mL) was 18.4±9.0ng/ml (men: 18.9±9.7, women: 18.2±8.9).Prevalence of hypovitaminosis D [25(OH) D < 30ng/mL] was 91.6%. 18.58% (55/296 patients) had severe deficiency of vitamin D. Of the 257 patients that reported at the end of six and nine months of treatment with cholecalciferol, 217 (84.4%) were symptom free.**Conclusion:** Hypovitaminosis D should be considered at number one in the differential diagnosis of patients presenting with diffuse musculoskeletal pain. Patients may be empirically treated with recommended doses of cholecalciferol where facilities for estimation of 25(OH) D are not available.
Keywords: Musculo- skeletal pains, Vitamin D deficiency, Cholecalciferol

Introduction

Chronic musculoskeletal pain is a common presenting complaint in out-patient clinics. Approximately one-third of the adolescents and one-half of adults suffer from this disorder. [1,2]Various studies conducted recently have found high (up to 93%) prevalence of hypovitaminosis D in such patients.[1,3,4]Most patients with diffuse musculoskeletal pain are initially suspected to be having rheumatic disorders, somatoform disorders and psycho-somatic disorders but hypovitaminosis D is not included in the differential diagnosis. The correct diagnosis is, therefore, delayed for long periods of time.[5]Though hypovitaminosis D was

documented as a case of chronic pain 30 years back in United Kingdom among immigrant populations, it is thought to be rarity in India country because of abundant sunshine. [6]Major part of Himachal Pradesh, a state located in sub-Himalayan region, falls in temperate and sub-temperate climatic zones where winter prevails for 3-9 months in a year. Out of a total area of 55,673 square kilometres, 37,033 square kilometres (66.5%) is covered by forests hampering the access to direct sunlight.[7]Inhabitants of temperate areas are more likely to keep their bodies covered with woollen clothing during the winters and are less likely to be exposed to the sunlight due to covered body parts and also due to absence of sun during the rainy and snow season. Moreover, most of the field work in the rural area is either done in the morning hours (from 5am-9am) and late after- noon (4pm-7pm) and urban population is mostly indoor (either in office and or doing indoor house- hold activities).Therefore, we conducted this study to estimate the prevalence of hypovitaminosis-D in one sub-set of population i.e. patients presenting with diffuse muscular-skeletal pain.

Objectives

- To estimate the prevalence of hypovitaminosis D among patients presenting with diffuse musculoskeletal pain.
- To determine socio-demographic factors associated with hypovitaminosis D.

Methodology

We conducted this cross-sectional study in adult (≥18 years) patients presenting with diffuse musculoskeletal pain (upper limb, shoulder girdle, lower limb, pelvic girdle, low back pain, chest wall pain) to out-patient clinic of the department of Internal medicine, Indira Gandhi Medical College & Hospital (IGMC), Shimla, from May 1, 2008 through April 30, 2011. The IGMC Shimla is an apex tertiary care institute of the sub-Himalayan state of Himachal Pradesh and caters to the needs of patients from most parts of the state. Himachal Pradesh is almost wholly mountainous with altitudes ranging from 350 meters to 6,975 meters above the mean sea level. Its location is between latitude 30º 22′40″ N to 33° 12′40″ N and longitude 75º 45′ 55″ E to 79º 04′ 20″ E. Physico-graphically, nine of the 12 districts in the state fall in temperate or sub-temperate climatic zones.[7]At the base line interview, participants were asked questions about shoulder and pelvic girdles, upper and lower extremity and back pain. If participants reported back and extremity pain almost every day during previous six months, they were asked to rate their pain uses a numeric pain rating scale, using number from 0 to 10 with 0 indicating no pain and 10 indicating the worst pain. To elicit tenderness, a firm thumb pressure sufficient to occlude capillary pressure on sternum and or on anterior tibia were applied; a Vince on the face indicates tenderness due to osteomalacia. [8]We excluded patients with known causes of musculoskeletal pain and those in whom a patho-physiological process could alter 25(OH) D levels/metabolism. Therefore, we excluded patients who were homebound due to some reason or were suffering from chronic diseases of liver, kidney, skin, heart or lungs, chronic anaemia, cancers, thyroid disease, alcoholics, pregnant women, patients with clinical conditions causing mal-absorption of nutrients (inflammatory bowel disease, Celiac disease, chronic pancreatitis and intestinal TB) and patients taking anti-convulsant or antitubercular therapy. We also excluded individuals that gave history of consuming vitamin D supplements during a period of six months prior to the enrolment in the study. We obtained written informed consent from each participant before subjecting him/her to clinical examination and laboratory investigations. All patients that were found to have hypovitaminosis D were treated with oral cholecalciferol 60,000 IU once a week for 8 weeks followed by 60,000 IU every two weeks.[8]Patients were asked to come for review at 3, 6, and 9 months after the start of treatment to evaluate the treatment outcome. Women aged more than 50 years and men aged more than 60 years were also given 1000mg/day elemental calcium. Operational definitionsfor 25-hydroxyvitamin D levels were as follows: <5 ng/mL = profound deficiency; 5.0-8.9 ng/mL = severe deficiency; 9.0-12.9 ng/mL = moderately severe deficiency; 13-16.9 ng/mL = moderate deficiency; 17-19.9 ng/mL = marginal deficiency; 20-29.9 ng/mL = insufficiency; <30 ng/mL = hypovitaminosis D.[3] After obtaining informed consent, a detailed history, a thorough general physical examination and a

focused systemic and neurological examination was done to rule out neuropathies and muscle disorders. Morning blood samples were obtained from the patients after an overnight fast (minimum 8 hrs fasting), for routine tests (complete haemogram, liver and kidney functions, electrolytes, calcium, phosphorous, albumin, alkaline phosphates, blood sugar and thyroid functions) and serum 25(OH)D. All biochemical tests were performed with auto-analyzer (Hitachi, Tokyo, Japan) on the same day of sample collection. Samples for 25(OH) D were stored at -20° C till analysis. Serum 25(OH) D was measured by radioimmunoassay (RIA). We analyseddata using EpiInfo Software version 3.5.3 for windows. We conducted descriptive analysis to calculate frequencies and percentages of each of the variable recorded. We calculated prevalence (%) of different grades of 25 (OH) D deficiencies and constructed 95 percent confidence intervals (C.I.) around the point estimates. We conducted bi-variate analysis to look at the selected determinants of 25 (OH) D deficiencies. We compared proportions by uncorrected chi-square test. For quantitative variables, we calculated means and standard deviations and compared them by student t-test. We considered p-value of 0.05 and below as statistically significant.

Results

We surveyed 296 patients who met the inclusion criteria. Of these 231 (78.0%) were women. The age of the study participants ranged from 19-78 years with a mean of 45.6±13.9 years (men: 47.3±13.4 years; women: 45.1±14.0 year). Participants from rural areas comprised 218 (73.6%) of the study population (Table 1).

The mean duration of symptoms was 37.4 months (Range: 7 months-11yrs). Eighty three (28%) patients sought consultation for the first time, while 213 (72%) patients had 2-7 consultations with other care providers before presenting to this institution. All patients, who had visited their primary care providers previously, were prescribed different combinations of non-steroidal anti-inflammatory drugs, antidepressants, anxiolytics and injection methylcobalamin without long term relief. The levels of 25(OH) D ranged from 1.7 ng/mL to 64.4 ng/mL. Mean 25(OH) D level (ng/mL) was 18.4±9.0 (men: 18.9±9.7, women: 18.2±8.9). There was no difference in the mean 25(OH) D levels by gender (p=0.602). Median 25(OH) D level was 18.3 ng/mL (inter-quartile range: 12.2-23.5 ng/mL). Only one patient had 25 (OH) D levels higher than 50 ng/mL (Fig. 1).

Prevalence of hypovitaminosis D [25(OH) D < 30ng/mL] was 91.6%. Whereas 59.5% of the patients had deficiency of vitamin D and another 32.1% of the patients demonstrated insufficient levels of 25-OH vitamin D in their sera. Of all patients 18.58% (55/296 patients) had severe deficiency of vitamin D (<10ng/ml) including 56% of whom were younger than 30 years. Only 8.4% of all participants (10.8% men and 7.8% women) had normal 25-OH vitamin D levels (Table 2).

We did not find any association of 25(OH) D levels with age, sex, place of residence or economic status (Tables 3 & 4). However, there was an inverse relationship between severity of symptoms and serum 25(OH) D concentration with most severe pain below serum concentration <15.0 ng/mL.

Of the 257 patients that reported at the end of six and nine months of treatment with cholecalciferol, 217 (84.4%) were symptom free. Response to treatment started at three month with maximum response seen at six month in 189 (87.09%) patients of total 217 patients who came for follow-up. A strong inverse relationship between severity of symptoms, serum 25 (OH) D concentrations and response to treatment was observed.

Discussion

The prevalence of hypovitaminosis D was found to be very high in patients with diffuse non-specific musculoskeletal pains in this study. There was no association of age, sex, place of residence (rural/urban) and socio-economic status with deficiency/insufficiency of vitamin D. (p>0.05). India is largely a tropical country extending from 8.4° N latitude to 37.6° N latitude. Inspite of ample sunshine in the plain areas of the country, vitamin D deficiency has been found to be common in all age groups and in both sexes.[9-11]All studies conducted in India, however, are from non-temperate/tropical regions and among different target populations. Most studies that examined the association between vitamin D levels and diffuse non-specific muscular pain were conducted

outside India. These studies generated a substantial body of evidence that implicates vitamin D deficiency in non-specific musculoskeletal pain.[3,12-16] Plotnik off GA, Quigley JM[3] from USA (Minneapolis) and AbbasiM, et al [17] from Iran studied 150 and 60 patients respectively with diffuse musculoskeletal pain and found 93% and 95.4% of the patients had vitamin D deficiency. However, in a study by Heidari B, et al[18] among 265 patients with musculoskeletal pain, 63.4% had vitamin D deficiency. However, it is difficult to compare our study directly with these studies given the differences in the study population (our patients belong from both rural and urban areas of the state from very large geographical region of the state with different socioeconomic profile) and in operational definition of vitamin D levels in which we included insufficiency level on our study. Our justification to include vitamin D insufficiency is based on the recent literature that showed serum 25 (OH) D levels of 30 ng/mL are required for normalization of elevated parathyroid hormone (PTH) level as a threshold for optimal bone and muscle function.[8,19]Phosphaturic effect of elevated PTH with diminished absorption of calcium from GI leads to abnormal calcium-phosphorus product leading to diminished mineralization of collagen matrix of bone. Instead, the demineralised matrix hydrates and expands and creates an outward pressure on thoroughly innervated periosteum and causing throbbing pain.[8] Our study confirmed that vitamin D supplementation relieve the pain in majority of patients.[17, 20]In our study there was a strong inverse relationship between serum 25 (OH) D concentrations and severity and duration of symptoms. Similar observations were made by Erkal MZ, et al.[4]Also a strong inverse relationship between baseline serum 25 (OH) D levels and response to supplement vitamin D was seen in our study. Similar observation was seen by Abbasi M et al.[17] Although it is unclear to what extent environment and or/ genetic factor are responsible for high prevalence of hypovitaminosis D in our study participants, however, inadequate direct sun exposure, dark pigmentation, traditional diet poor in vitamins D, no vitamin D food fortification in our country and traditional use of whole body covering cloths along with head scarf added by living at high northern latitude are the possible explanation for this high prevalence.

Conclusions and recommendations

Hypovitaminosis D should be considered at number one in the differential diagnosis of patients presenting with diffuse musculoskeletal pain at least in areas falling in temperate/sub-temperate climatic zones. As toxicity is rare with oral therapeutic doses of vitamin D,the patients may be empirically treated with recommended doses of cholecalciferol where facilities for estimation of 25(OH) D are not available. Community based studies need to be undertaken to estimate the prevalence of hypovitaminosis D in the sub-Himalayas to make a case for food- fortification with Vitamin D.

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Table 1: Socio-demographic and biochemical profile of study population (n=296)

S.No.	Characteristic/Variable	No.	%
1	**Age group (years)**		
	<25	32	10.8
	25-34	48	16.2
	35-44	54	18.2
	45-54	85	28.7
	55-64	56	18.9
	≥65	21	7.1
2	**Sex**		
	Women	231	78.0
	Men	65	22.0
3	**Place of residence**		
	Rural	218	73.6
	Urban	78	26.4
4	**Income (INR/Rupees)**		
	≥ 5000	177	59.8
	< 5000	119	40.2

Table 2: Prevalence of different grades of hypovitaminosis D in the study population

Vit D (25-OH D) status	Men (n=65)			Women (n=231)			Total (n=296)		
	No.	%	95% CI*	No.	%	95% CI	No.	%	95% CI
Hypovitaminosis any grade (<30 ng/ mL)	58	89.2	79.1-95.6	213	92.2	88.0-95.3	271	91.6	87.8-94.5
Insufficiency(20-29.9 ng/ mL)	22	33.8	22.6-46.6	73	31.6	25.7-38.0	95	32.1	26.8-37.7
Deficiency (<20 ng/ mL)	36	55.4	42.5-66.7	144	60.6	54.0-67.0	176	59.5	53.6-65.1
Marginal deficiency (17.0-19.9 ng/mL)	10	15.4	7.6-26.5	31	13.4	9.3-18.5	41	13.9	10.1-18.3
Moderate deficiency (13.0-16.9 ng/mL)	10	15.4	7.6-26.5	41	17.7	13.0-23.3	51	17.2	13.1-22.0
Moderately severe deficiency (9.0-12.9 ng/mL)	5	7.7	2.5-17.0	32	13.9	9.7-19.0	37	12.5	9.0-16.8
Severe deficiency (5.0-8.9 ng/mL)	7	10.8	4.4-20.9	26	11.3	7.5-16.1	33	11.1	7.8-15.3
Profound deficiency (<5 ng/ mL)	4	6.2	1.7-15.0	10	4.3	2.1-7.8	14	4.7	26.0-7.8
Normal (≥30 ng/ mL)	7	10.8	4.4-20.9	18	7.8	4.7-12.0	25	8.4	5.5-12.2

*CI (Confidence Interval)

Table 3: Comparison of mean 25-OH Vit D levels by selected socio-demographic characteristics

Variable	25-OH Vit D (ng/mL)			p-value
	Mean	s.d.*	SEM†	
Sex				
Women	18.21	8.85	0.582	0.602
Men	18.87	9.65	1.196	
Age group (years)				
≥ 50	19.19	8.54	0.709	0.120
<50	17.56	9.42	0.766	
Place of residence				
Urban	17.51	8.48	0.624	0.336
Rural	18.66	9.21	0.960	
Income (INR per month)				
< 5.000	19.08	8.72	0.69	0.258
≥ 5000	17.87	9.21	8.72	
Women				
Reproductive age group (15-49 years) grou	17.33	8.81	0.791	1.049
≥ 50	19.22	8.84	0.855	

*s.d.=standard deviation; †SEM: Standard Error of the Mean.

Table 4: Bivariate analysis: prevalence of hypovitaminosis D according to selected socio-demographic characteristics.

Exposure	Prevalence of Hypovitaminosis D (<30ng/mL)						Prevalence ratio	95% CI*	p-value
	Among exposed			Among unexposed					
	#	Total	%	#	Total	%			
Female sex	213	231	92.2	58	65	89.2	1.03	0.94-1.13	0.446
Age ≥ 50	132	145	91.0	139	151	92.1	0.99	0.92-1.06	0.753
Urban Residence	72	78	92.3	199	218	91.3	1.01	0.94-1.09	0.780
Low income (<INR 5.000/- per month)	105	119	88.2	166	177	93.8	0.94	0.87-1.02	0.092

*CI (Confidence Interval)