

ORIGINAL ARTICLE

Vitamin D level among patients with unexplained musculoskeletal symptoms

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ABSTRACT

Background: Unexplained musculoskeletal (MSK) symptoms sometimes pose diagnostic and management challenges and can lead to prolonged suffering and disability. Hypovitaminosis D could be a reason for such symptoms. This study aimed to determine the vitamin D level among patients with unexplained MSK symptoms.

Methods: A cross-sectional study was conducted in a private clinic of Chattogram city, Bangladesh. A total of 110 unexplained MSK patients were enrolled conveniently. MSK symptoms were assessed by rheumatologist and serum vitamin D levels were measured according to the standard laboratory procedure. Descriptive and logistic regression analyses were done. Principal component analysis was performed for the reduction of MSK symptoms.

Results: The median (interquartile range) vitamin D level was 24.6 (20.0–29.0) ng/mL. Hypovitaminosis D (<30 ng/mL) was observed in 80.0% (95% CI: 71.3%–87.0%) respondents. Patients who had difficulty in climbing stairs, bone pain and muscle cramp had 79.8%, 84.9% and 79.8% hypovitaminosis D respectively. In logistic regression analysis, overweight defined by body mass index ≥ 25 kg/m² (OR 5.5, 95% CI 1.7–17.4) was significantly associated with hypovitaminosis D.

Conclusions: Hypovitaminosis D was common in patients with unexplained MSK symptoms and overweight was significantly associated with it. Further studies in representative samples are necessary.

Keywords: Vitamin D, hypovitaminosis D, unexplained MSK symptoms, musculoskeletal symptoms

INTRODUCTION

Musculoskeletal (MSK) symptoms encompass a wide range of clinical presentations, including pain, stiffness, and weakness affecting the muscles, bones, and joints.¹ These symptoms pose diagnostic challenges due to their diverse etiologies, often leading to prolonged suffering and disability for patients.² Occasionally some MSK symptoms cannot be explained by any specific MSK disease and refers as non-specific or unexplained MSK symptoms. The complexity of unexplained MSK symptoms necessitates further exploration of potential contributing factors, including nutritional deficiencies, such as low levels of vitamin D.³

Vitamin D, a secosteroid hormone synthesized in the skin upon sunlight exposure and obtained through dietary sources, plays a pivotal role in maintaining

skeletal health and various physiological processes.⁴ It exerts pleiotropic effects on bone metabolism, immune modulation, muscle function, and overall well-being. Deficiency or insufficiency of vitamin D has been implicated in the pathogenesis of several musculoskeletal disorders, including osteoporosis, osteomalacia, and muscle weakness.⁵ Consequently, assessing the vitamin D status among patients with unexplained MSK symptoms may offer valuable insights into the underlying mechanisms of these symptoms.^{6,7}

Usually, adults with vitamin D deficiency typically exhibit various MSK symptoms, including bone pain, muscle weakness, muscle spasm, muscle cramp.⁸ The MSK manifestations of vitamin D deficiency may include joint discomfort, fatigue, walking difficulties with or without stair climbing, and difficulty rising from a squatting position.⁷

HIGHLIGHTS

1. Vitamin D deficiency in adults usually presents with various MSK symptoms like bone pain, muscle weakness, muscle spasm, muscle cramp.
2. Eight out of ten patients with unexplained musculoskeletal symptoms had hypovitaminosis D (< 30 ng/mL).
3. Overweight (body mass index ≥ 25 kg/m²) was found to be significantly associated with hypovitaminosis D.
4. Vitamin D level and body composition can be considered while treating unexplained MSK symptoms.

In Asia, vitamin D deficiency is more prevalent.⁹ A study conducted at tertiary hospital in Dhaka, Bangladesh discovered that 86% of participants had hypovitaminosis D.¹⁰ Therefore, measurement of serum vitamin D level in patients with unexplained MSK symptoms may give a diagnostic clue as well as the patients would be benefited with simple treatment in case of vitamin D deficiency.

To date, there is a dearth of scientific research conducted in Bangladesh concerning the assessment of vitamin D levels among individuals experiencing unexplained MSK symptoms. Therefore, exploring the vitamin D level and the potential associated factors of vitamin D deficiency among patients with unexplained MSK can contribute to enhancing diagnostic accuracy and optimizing treatment strategies.

We aimed to determine the vitamin D level among patients with unexplained MSK symptoms. Moreover, we seek to explore potential associated factors for hypovitaminosis D within the study subjects.

METHODS

Study design and population

This cross-sectional study was done during July 2018 to December 2019 in Chevron clinical laboratory, Chattogram, Bangladesh. Patients aged 18 and above who presented with MSK symptoms and for which a clear etiology could not be determined were included. The sample size was determined considering the prevalence of previous study¹⁰ and found 185. However finally, we ended up with 110 patients, and their serum vitamin D was measured. Detailed demographic information including age, sex, education, height and

weight was collected. Body Mass Index (BMI) was calculated from weight and height. Specific physical status indicators such as muscle weakness, muscle cramp, difficulty in climbing stairs, fatigue, difficulty in squatting, pain in weight-bearing joints, bone pain was noted. Patients having active arthritis, myopathy, connective tissue diseases, trauma, disabilities were excluded through comprehensive clinical, radiological, and laboratory examinations. Other exclusion criteria were renal impairment, liver disease, active infection, pregnancy and patients who were using vitamin D supplementation. Any study subjects with missing data were excluded during analysis. Informed written consent was obtained from all participants before their enrollment into the study.

Data collection

Data collection was performed using a semi-structured questionnaire designed specifically for this study. Blood samples were collected from cubital vein by using regular red-top Vacutainers. Vitamin D analysis was done from fresh serum. Beckman Coulter Access-2 Analyzer was used to measure 25-hydroxy vitamin D total (vitamin D₂ and D₃) by using the Chemiluminescent Immunoassay method. Hypovitaminosis D was defined as a serum vitamin D level below 30 ng/mL.¹¹

Ethical issues

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and we assured that the data would be used for scientific research only. This study was approved by the Institutional Review Board of the Chattogram Maa-O-Shishu Hospital Medical College. Written informed consent was taken from all the patients before taking part of the study.

Statistical analysis

Data were analysed by using Statistical Product and Service Solutions for windows, version 26. Mean, standard deviation, median, interquartile range,

number and percent were used to describe the data. *t* test for quantitative data, chi-square and Fisher's exact tests for categorical data were employed to evaluate the differences between normal vitamin D levels and hypovitaminosis D. Three out of seven musculoskeletal symptom variables were identified using principal component analysis (PCA). Eigen values greater than 1 were considered to select variables. Univariate and multivariate logistic regression analyses were done to identify potential factors associated with hypovitaminosis D among patients with unexplained MSK symptoms. $P < 0.05$ was considered statistically significant.

RESULTS

Out of the 110 participants included in the study, 79 (71%) were women. The mean (standard deviation) age was 46.5 (12.8) years, with no significant differences observed between men and women. The majority of respondents (60.9%) fell within the age range of 18 to 49 years. Around 40% of the participants had an education level below higher secondary, and 90% were overweight (body mass index ≥ 25 kg/m²) (TABLE 1).

Regarding MSK symptoms approximately 95% reported muscle cramp, four-fifth experienced difficulties in climbing stairs and two-third reported bone pain (TABLE 1). Muscle weakness was reported by approximately 95% of the participants, followed by fatigue (79%), difficulties in squatting (76%), and pain in weight-bearing joints (73%).

The median (inter quartile range) vitamin D level was 24.6 (20.0–29.0) ng/mL. Although not statistically significant ($P = 0.056$), men had a slightly higher mean vitamin D level (26.5 ng/mL) compared to women (23.8 ng/mL). The overall prevalence of hypovitaminosis D among the patients was 80% (95% CI: 71.3%–87.0%) with 82.3% of women and 74.2% of men being affected. Notably, patients who were overweight (≥ 25 kg/m²) exhibited a significantly higher prevalence of hypovitaminosis D ($P = 0.004$) (TABLE 1). Hypovitaminosis D was highest observed among the patients with bone pain (85%) and difficulties in squatting (85%), followed by pain in weight bearing joints (81.3%), muscle weakness (80.8%), fatigue (80.5%), muscle cramp (79.8%) and difficulties in climbing stairs (79.8%).

TABLE 1 Sociodemographic status and vitamin D level in patients with unexplained musculoskeletal symptoms

Characteristics	Vitamin D level (ng/mL)	Total n=110	Normal (≥ 30 ng/mL)	Hypovitaminosis D (< 30 ng/mL)	<i>P</i> ^a
	Median (IQR) ^b	n (%)	n (%)	n (%)	
Age in years ^c	-	46.5 (12.8)	47.0 (13.0)	46.4 (12.8)	0.85
Age groups, years					
18–49	23.5 (19.0–27.0)	67 (60.9)	10 (14.9)	57 (85.1)	0.10
≥ 50	25.0 (21.0–30.0)	43 (39.1)	12 (27.9)	31 (72.1)	
Sex					
Men	25.0 (22.3–30.0)	31 (28.2)	8 (25.8)	23 (74.2)	0.34
Women	23.0 (19.0–27.0)	79 (71.8)	14 (17.7)	65 (82.3)	
Education					
Below higher secondary	25.0 (21.0–29.0)	48 (43.6)	8 (16.7)	40 (83.3)	0.44
Higher secondary or above	24.2 (19.0–28.0)	62 (56.4)	14 (22.6)	48 (77.4)	
Body mass index					
<25 kg/m ²	27.0 (21.0–31.0)	21 (19.1)	9 (42.9)	12 (57.1)	0.004
≥ 25 kg/m ²	24.0 (20.0–27.0)	89 (80.9)	13 (14.6)	76 (85.4)	
Musculoskeletal symptoms ^d					
Difficulties in climbing stairs					
Yes	25.0 (20.0–29.0)	89 (80.9)	18 (20.2)	71 (79.8)	0.90
No	24.0 (21.0–27.0)	21 (19.1)	4 (19.1)	17 (81.0)	
Bone pain					
Yes	23.0 (20.0–26.2)	73 (66.4)	11 (15.1)	62 (84.9)	0.07
No	26.0 (22.0–31.6)	37 (33.6)	11 (29.7)	26 (70.3)	
Muscle cramp					
Yes	25.0 (20.5–29.0)	104 (94.6)	21 (20.2)	83 (79.8)	0.83
No	18.5 (18.0–28.0)	6 (5.4)	1 (16.7)	5 (83.3)	

^a*P* value is normal versus hypovitaminosis D; all are chi-square test except bold is Fisher's exact test, age in years *t* test; ^bIQR: Interquartile range; ^cMean (standard deviation)

^dMuscle weakness, fatigue, difficulties in squatting and pain in weight-bearing joints were not reported as the eigenvalues less than one in principal components analysis

PCA revealed three components that had eigenvalues greater than one and which explained 28.3%, 19.0% and 14.6% of the total variance, respectively. The three components solution explained 61.9% of the total variances where 'difficulty in climbing stairs', 'bone pain' and 'muscle cramp' scored highest in each component respectively (TABLE 1).

Multivariate logistic regression analysis, incorporating age, sex, education, body mass index, difficulties in climbing stairs, bone pain and muscle cramp in the model, identified overweight (body mass index ≥ 25 kg/m²) (OR 5.5, 95% CI 1.7–17.4) as a significant predictor of hypovitaminosis D (TABLE 2).

DISCUSSION

Key Findings

We aimed to investigate the vitamin D levels among patients with unexplained musculoskeletal (MSK) symptoms. The results revealed that, the prevalence of hypovitaminosis D among the study participants was remarkably high (80%). This study identified

overweight (BMI ≥ 25 kg/m²) as a significant predictor of hypovitaminosis D. PCA revealed three out of seven MSK symptoms such as difficulties in climbing stairs, bone pain, and muscle cramp scored highest in each component.

Strengths and limitations

This study has several strengths, including the comprehensive assessment of musculoskeletal symptoms among patients with unexplained MSK symptoms. The study utilized standardized laboratory methods to measure serum vitamin D levels, ensuring the reliability of the results. Additionally, the study considered various potential confounding factors, ruling out conditions such as active arthritis, myopathy, connective tissue diseases, trauma, and disabilities through comprehensive clinical, radiological, and laboratory examinations by the researcher.

However, several limitations should be acknowledged. First, we could not come up with the estimated sample size and the samples were selected conveniently and from a city based private clinic. Therefore, the study has a limitation of adequate power of the statistical tests and generalizability. Second, the cross-sectional design of the study limits causal inferences. Longitudinal studies are necessary to establish temporal relationships between vitamin D levels and musculoskeletal symptoms.

Comparison with similar researches

The high prevalence of hypovitaminosis D observed in our study is in line with studies conducted in Iran (95.4%) and Hongkong (84.1%) as most of the patients had vitamin D deficiency.^{12, 13} As we observed that overweight (BMI ≥ 25 kg/m²) was a significant predictor of hypovitaminosis D among patients with unexplained MSK symptoms however, previous studies that also demonstrated a relationship between higher body mass index and lower vitamin D levels.¹⁴ Adipose tissue can sequester vitamin D, leading to reduced circulating levels in individuals with excess body fat.¹⁵ Therefore, the observed association between overweight status and hypovitaminosis D highlights the importance of considering body composition as a potential risk factor in patients with unexplained MSK symptoms.

TABLE 2 Univariate and multivariate analysis between vitamin D status and sociodemographic, musculoskeletal symptoms (n=110)

Variables	Univariate OR (95% confidence interval)	Multivariate ^a OR (95% confi- dence interval)
Age groups, years		
18–49	Reference	Reference
≥ 50	0.5 (0.2–1.2)	0.4 (0.1–1.1)
Sex		
Men	Reference	Reference
Women	1.6 (0.6–4.3)	0.8 (0.2–2.9)
Education		
Below higher secondary	Reference	Reference
Higher secondary or above	1.5 (0.6–3.8)	2.0 (0.6–6.0)
Body mass index		
<25 kg/m ²	Reference	Reference
≥ 25 kg/m ²	4.4 (1.5–12.5) ^b	5.5 (1.7–17.4) ^b
Musculoskeletal symptoms		
Difficulties in climbing stairs		
No	Reference	Reference
Yes	0.9 (0.3–3.1)	0.7 (0.2–2.5)
Bone pain		
No	Reference	Reference
Yes	2.4 (0.9–6.2)	2.0 (0.7–6.2)
Muscle cramp		
No	Reference	Reference
Yes	0.8 (0.1–7.1)	0.7 (0.1–8.2)

^aModel included age, sexes, education, body mass index, difficulty in climbing stairs, bone pain and muscle cramp simultaneously; ^bP<0.05

Explanations of findings

The high prevalence of hypovitaminosis D among patients with unexplained MSK symptoms observed in our study warrants further explanation. Vitamin D deficiency is often asymptomatic, but it can manifest as muscle cramps and bone pain.¹⁶ In line with these findings, we observed that the highest percentage of patients experiencing muscle cramps had low vitamin D levels. Other studies have also reported an association between vitamin D deficiency and proximal myopathy, with more pronounced effects observed at vitamin D levels below 10 ng/mL.¹⁷ Muscle weakness and pain, which can be attributed to vitamin D deficiency, have been documented in both adults and children.¹⁸

Difficulty in climbing stairs is a symptom commonly associated with proximal muscle weakness. Interestingly, in our study, we did not find any patients with rheumatic or neurological diseases who had difficulty climbing stairs. This may be explained by the presence of vitamin D deficiency or insufficiency, which can contribute to muscle weakness and compromise physical function.¹⁹

The underlying mechanisms of bone-associated pain in humans and animals are not fully understood. Bone disorders such as osteoporosis, characterized by decreased bone density and increased fragility, can lead to bone-associated pain. Animal models are being utilized to investigate the mechanisms of pain and develop improved treatments.²⁰ Serum 25-hydroxy vitamin D deficiency has a possible contributory role for the development of pain and tenderness over the tibial bone.²¹ The intensity of bone pain is directly related to vitamin D deficiency.²² In our study, approximately two-thirds of the patients reported experiencing bone pain, and 85% of them had low vitamin D levels.

The correlation between bone pain intensity and vitamin D deficiency further supports the role of vitamin D in bone health. Adequate vitamin D levels are crucial for maintaining bone health and reducing the risk of skeletal complications.²³ The observation that a substantial proportion of patients with bone pain in our study had low vitamin D levels strengthens the evidence for the association between vitamin D deficiency and bone-related symptoms.

Obesity demonstrated as a risk factor for hypovitaminosis D among patients with unexplained MSK symptoms. This finding aligns with the common observation of hypovitaminosis D among obese individuals. One possible explanation is the volumetric dilution of vitamin D concentration into the larger volumes of fat, serum, liver, and muscle in obese subjects. This phenomenon can contribute to lower levels of bioavailable vitamin D and subsequently lead to hypovitaminosis D in individuals with obesity.²⁴

Implications and actions needed

Taken together, the findings of our study have important implications for clinical practice and public health. Given the high prevalence of hypovitaminosis D among patients with unexplained MSK symptoms, it is crucial to include vitamin D assessment as part of the diagnostic workup for individuals presenting with musculoskeletal symptoms. Further research is needed to elucidate the precise mechanisms underlying these associations and to explore the potential benefits of vitamin D supplementation in managing musculoskeletal symptoms in this patient population. The association between overweight status and hypovitaminosis D highlights the need to consider body composition, particularly obesity, as a potential risk factor for vitamin D deficiency among patients with unexplained MSK symptoms.

Conclusion

Hypovitaminosis D was quite common in patients with unexplained MSK symptoms and overweight associated with it. Therefore, highlighting the importance of considering Hypovitaminosis D and body composition while treating unexplained MSK symptoms. Further studies in representative samples are necessary.

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Author Contributions

Conception and design: MAR, IHB, RB. Acquisition, analysis and interpretation of data: MAR, IHB, RB. Manuscript drafting and revising it critically: MAR, IHB, RB, MZH, MNK, MRC. Approval of the final version of the manuscript: MAR, IHB, RB, MZH, MNK, MRC. Guarantor accuracy and integrity of the work: MAR, IHB, RB.

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Conflict of Interest

No author has any conflict of interest to disclose for this manuscript. The authors themselves are responsible for their ideas and views expressed in this article, which do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of the Chattogram Maa-O-Shishu Hospital Medical College (CMOSHCITRB/2018/04). Written informed consent was taken from all the patients before taking part of the study.

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