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**Dr. Arshdeep S Mann**  
MBBS, Medical Officer, Maan  
Hospital and Dialysis Center,  
Bathinda, Punjab, India

**Dr. Harmanjot Singh**  
MBBS, MD, Internal  
Medicine, ECFMG,  
Washington Medical Board,  
USA

**Dr. Beant Singh Maan**  
MBBS, MD, Internal  
Medicine, Medical Director,  
Maan Hospital and Dialysis  
Center, Bathinda, Punjab,  
India

**Corresponding Author:**  
**Dr. Arshdeep S Mann**  
MBBS, Medical Officer, Maan  
Hospital and Dialysis Center,  
Bathinda, Punjab, India

## To study the association of serum vitamin D levels with migraine in Indian rural female population: Case-control study

**Dr. Arshdeep S Mann, Dr. Harmanjot Singh and Dr. Beant Singh Maan**

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### Abstract

**Aim:** To investigate the vitamin D serum levels of migraine patients and compared it with a control group.

**Materials and Methods:** The present case control study entitled was conducted in the Department of General Medicine during the period of I year. The study was performed on 150 female patients (case group n = 100 and matched control group n = 50) attended General Medicine outpatient department. 25-hydroxy vitamin D was analyzed with liquid chromatography-tandem mass spectrometry (LC/MS/MS) method.

**Results:** The Mean Age, Serum vitamin D level and BMI among cases and controls are as follows (34.54±1.37, 33.17±1.19), (13.12±0.98, 13.41±0.19) and (26.4±1.21, 25.8±1.53). 58% of the cases had migraine frequency per month of more than 10 episodes and 36% of the cases shown that the pain last for 4-12 hours in a day.

**Conclusion:** The prevalence of vitamin D deficiency is roughly similar between cases and controls and between matching age groups. This suggests a high prevalence of vitamin D deficiency in both healthy population and migraine patients which implies a common underlying cause.

**Keywords:** Serum vitamin D, migraine headache, female.

### Introduction

Vitamin D has been discovered at the beginning of the 20th century as a cure for rickets, a disease softening the bones in children <sup>[1, 2]</sup>. Since then it has been established as an important factor in bone health, more specifically in bone metabolism and calcium homeostasis. Vitamin D is a lipid soluble vitamin which has a function of a hormone in the human body <sup>[3]</sup>. There are two forms of vitamin D present in nature: Vitamin D<sub>2</sub> (ergocalciferol) and vitamin D<sub>3</sub> (cholecalciferol) <sup>[2]</sup>.

Vitamin D is not only important in mineral homeostasis but it is also an anti-inflammatory hormone that can regulate immune responses, cell proliferation, and endothelial function <sup>[4, 5]</sup>. Also, vitamin D has a negative effect on proliferation of mast cells and can stimulate nitric oxide (NO) <sup>[6]</sup> (a vasoactive substance that interacts with blood vessels). With these mechanisms, vitamin D has a potent role in cardiovascular disease <sup>[7]</sup>. Growing but conflicting evidence has shown a possible relationship between vitamin D and chronic or recurrent painful conditions such as migraine <sup>[8]</sup>.

There are no known causes of migraines that are consistent for all patients. However, there are some common causing factors that are found amongst migraines. Some of those factors are depicted as hyperexcitable brain that reacts stronger to stimuli, which happens due to an inflammation of the lining of the brain. Another factor is genetics, where people are more predisposed to changes in estrogen levels, weather changes, a disrupted sleep pattern, or red wine. (Evans & Evans 2009) <sup>[9]</sup>.

As of today, there is no known cure for migraine headaches. However, there are a few possible treatments for the symptoms of this disorder. One study reported that 40% of migraine patients had vitamin D deficiency <sup>[10]</sup>. Two case-report studies have shown that treatment with vitamin D and calcium in patients suffering from migraine dramatically reduced frequency and severity of migraine <sup>[11, 12]</sup>. Improvement of headache symptoms in eight vitamin D insufficient patients that had osteomalacia and tension-type headache (TTH) symptoms has been reported after they took vitamin D and calcium supplements for a short

period of time [13]. In molecular level, Motaghi *et al.* [14], have shown that vitamin D receptor polymorphisms are associated with migraine without aura and also headache severity.

However, there are no studies that compare vitamin D levels between control group and migraine patients with a large enough sample size and adjustments for age and sex. Also, there are no studies that compare the frequency and severity of headaches based on the vitamin D status. Therefore, in the view of above observations and paucity of data we investigated the vitamin D serum levels of migraine patients and compared it with a control group.

**Materials and Methods**

The present study entitled “To study the association of serum vitamin D levels with Migraine in Indian rural female population” was conducted in the Department of General Medicine during the period of 1 year. This observational case control study was performed on 150 patients (case group n = 100 and matched control group n = 50) attended General Medicine outpatient department.

**Inclusion criteria**

1. Patients who had given written and informed consent to take part in the study
2. Age group 18-50 years
3. Patients with Chronic Headache
4. Diagnosis of Migraine based on history, physical examination, Guidelines according to International classification of Headache Disorders-II and ruling out secondary causes of headache with the help of relevant investigations

**Exclusion criteria**

1. Patients with conditions like hypertension, seizures, ocular disorders like refractory error & Glaucoma, Intracranial space occupying lesions, head trauma, CVA, infections of sinuses, ear & CNS, metabolic derangements and other plausible causes of headache.
2. Age < 18 years or > 50 years.
3. Patients who refused to give consent.

**Data collection and Measurement**

Demographic data including Age, BMI, Serum Vitamin D level and Level of Education was obtained from both groups. Patients were evaluated with regard to their Headache duration and Headache frequency and filled out the migraine severity scale (MIGSEV). It is a simple severity scale which categorized patients in three groups of intensity; mild, moderate, and severe. This instrument is highly reliable, reproducible, and sensitive [15]. To measure serum vitamin D level 3 mL of venous blood was drawn from each participant and immediately centrifuged. Serum samples were then frozen and kept at minus 70 degrees centigrade. Then, samples for plasma levels of 25-hydroxy vitamin D were analyzed with liquid chromatography-tandem mass spectrometry (LC/MS/MS) method.

Based on previous studies and reports of Institute of Medicine (IOM), we considered serum levels of 25-hydroxy vitamin D of >20, 10–20, and <10 ng/mL as normal, insufficient, and deficient, respectively [16].

**Statistical analysis**

We analyzed our data with the SPSS software (version 18.0, Chicago, IL, USA). Mann-Whitney *U* test was used for the comparison of quantitative variables between two groups, since our data was not normally distributed. The sample size achieved 80% of the statistical power. Confidence level and level of significance were fixed at 95% and 5% respectively.

**Results**

**Table 1:** Mean values of age, serum Vit. D and BMI among cases and controls

Variables	Cases (N = 100)	Controls (N = 50)	p - value
Age (Mean ± SD)	34.54 ± 1.37	33.17 ± 1.19	0.292
Serum Vit. D	13.12 ± 0.98	13.41 ± 0.19	0.078
BMI	26.4 ± 1.21	25.8 ± 1.53	0.096

Test applied: Student t-test

**Table 2:** Demographic distribution of study participants

Variables	Cases N = 100 (%)	Controls N = 50 (%)
Age groups		
Less than 30 years	42 (42)	27 (54)
More than 30 years	58 (58)	23 (46)
Level of education		
Below high school	43 (43)	22 (44)
Above high school	57 (57)	28 (56)

**Table 3:** Distribution of cases according to headache frequency and duration

Variables	Cases N = 100
Frequency of headache (Per month)	
More than 10	58 (58)
Less than 10	42 (42)
Duration of headache (Per hour)	
4-12	36 (36)
12-24	21 (21)
24-72	16 (16)

**Table 4:** Distribution of different feature of migraine among cases

Variables	Cases N = 100 (%)
Intensity of pain	
Mild	9 (9)
Moderate	28 (28)
Intense	41 (41)
Very intense	22 (22)
Level of nausea	
None	16 (16)
Mild	39 (39)
Intense	23 (23)
Vomiting	22 (22)
Level of disability	
None	7 (7)
Mild	34 (34)
Marked	21 (21)
Confined to bed	38 (38)
Level tolerability	
Tolerable	19 (19)
Barely Tolerable	48 (48)
Intolerable	33 (33)
MIGSEV total	
Low	17 (17)
Intermediate	44 (44)
High	39 (39)

**Table 5:** Distribution of mean serum vitamin D levels according to demographics

Mean serum vitamin D levels				
Variables	Controls (N=50)	p - value	Cases (N= 100)	p - value
Age groups				
Less than 30 years	13.18 ± 0.36	0.843	13.02 ± 0.76	0.711
More than 30 years	13.85 ± 0.11		13.51 ± 0.19	
Level of education				
Below high school	13.11 ± 0.71	0.631	13.90 ± 0.38	0.881
Above high school	13.32 ± 0.62		13.24 ± 0.81	

Test applied: Student t-test

## Discussion

Based on our results, there was no significant difference in 25(OH)D plasma levels between cases and controls. Our analysis also did not show any relationship between 25(OH)D plasma levels and the severity of headaches among patients. Vitamin D deficiency has been defined based on various references. In most of the studies, 25(OH)D plasma levels lower than 10 ng/mg are considered deficient [17], but defining the threshold for the levels of vitamin D insufficiency is a controversial issue [18, 19].

IOM recommended the levels of 20 ng/mL (50 nmol/liter) covering the requirements of at least 97.5% of the population and this critical level will be useful for clinicians for patients' management [1]. Also, most of the studies reported that high majority of complications related to low levels of vitamin D such as hypoparathyroidism, bone fractures, and multiple sclerosis are becoming at levels below (20 ng/mL) [20].

The vitamin D plasma level can be measured by different laboratory methods including chemiluminescence assay, radioimmunoassay (RIA), and enzyme-linked immunosorbent assay (ELISA). Different methods can lead to significantly different reported levels of vitamin D in the same sample population. Inter-method variability of the 25(OH)D plasma levels can impact on further analysis of data from different studies. Data standardization is of great importance when different methods are used [21].

Kjaergaard *et al.* [22]. In a cross-sectional study with a large sample concluded that vitamin D is not related to migraine. The latter, however, is limited as it has used a questionnaire to identify patients rather than identifying them clinically. Questionnaires may miss the patients or over diagnose people with migraine. Also, in this study, the relationship between severity and frequency of headaches and vitamin D is not evaluated. Our results did not show any relation between vitamin D and either severity of the headaches or their frequency.

Some studies have suggested that higher latitudes are associated with more severe and frequent headaches and therefore can originate from lower 25(OH)D plasma levels due to diminished sun exposure. This conclusion, however, is not totally reliable as there are regions with lower latitudes and worse vitamin D status. It can be assumed that vitamin D insufficiency may be caused by a multiple factors and latitude alone may not be responsible for lower 25(OH)D plasma levels. Seasonal changes in 25(OH)D plasma levels are reported in the literature [18].

Thys-Jacobs reported dramatic reduction in frequency and duration of headaches after supplemental vitamin D administration. However, these results were from small case reports in two premenopausal and two postmenopausal

women without control group [24, 25]. Despite these results we did not find any relation between 25(OH)D plasma levels and menstrual related aggravation of headaches. The therapeutic effect of vitamin D supplementation is thought to be due to higher absorption of magnesium; however, these treatments were accompanied by calcium supplements also and the results could be attributed to both vitamin D and calcium or even the synergetic effect of the treatment.

Prakesh *et al.* [13]. reported positive effects of vitamin D and calcium supplements in tension type headache (TTH) patients. Beneficial outcomes of optimal 25(OH)D levels for TTH patients are also suggested by Keargaard *et al.* [22].

Prakash *et al.* [13]. reported high levels of parathyroid hormone (PTH) in migraine patients which could be due to secondary hyperparathyroidism that was treated by optimal levels of vitamin D supplement. The role of endothelial dysfunction and also the role of nitric oxide (NO) through vasodilatation as triggers for migraine headaches have been well established [23, 24]. There are also studies, claiming that there are higher levels of parathyroid hormone in the systemic circulation of patients with heart failure, which is associated with endothelial dysfunction [25]. Also, it is stated that PTH up regulates the activity of the endothelial nitric oxide synthase NOS system through protein kinase pathways [26].

On the other hand, vitamin deficiency can cause secondary hyperparathyroidism. However, whether or not the rise of PTH in this phenomenon contributes to worse migraine headaches through NO release and endothelial dysfunction is a matter of debate that needs further study.

Knutsen *et al.* [27]. Stated that vitamin D status has a much stronger relationship with headache rather than either musculoskeletal pain or fatigue. Our results did not reveal any relationship between the severity of the vitamin D deficiency and severity of the headaches. Also, 25(OH)D plasma levels were not different between MIGSEV items (nausea, intensity of pain, pain tolerability, and disability). The relationship between age and severity of vitamin D deficiency was established by Knutsen *et al.* [27]. We found no relation between the age and levels of 25(OH)D. Also, according to our results, vitamin D level was not related to level of education.

## Conclusion

The prevalence of vitamin D deficiency is roughly similar between cases and controls and between matching age groups. This suggests a high prevalence of vitamin D deficiency in both healthy population and migraine patients which implies a common underlying cause. It seems appropriate to conduct population-based observational studies to better assess the role of vitamin D in incidence, severity, and treatment of migraine headaches.

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