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Role of Serum Vitamin D Level in Migraine Headache in Jordanian Women: Case-Control Study

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Abstract **Case Report**

Background: Migraine is a prevalent and disabling primary headache disorder that has a major impact on quality of life. Recent literature has hinted towards a possible relationship between vitamin D insufficiency and the pathogenesis of migraine. However, there is limited information on this association in Jordanian women. ***Case Summary:*** This case-control study was conducted at one of the tertiary care hospitals in Amman, Jordan, Jordanian women, between March 2021 and March 2022, consisted of 50 female migraine patients (cases) and 50 age-matched healthy women (controls). Serum vitamin D was determined and compared between the groups. ***Key Findings:*** Mean serum vitamin D level of the migraine group was found to be significantly lower (14.3 ± 4.2 ng/mL) than the control group (23.7 ± 5.6 ng/mL) ($p < 0.001$). Vitamin D deficiency (<20 ng/mL) was also found in 80% of migraineurs compared with 42% of healthy subjects. The findings of this study indicate an inverse association between serum levels of vitamin D and occurrence of migraine. ***Conclusion:*** Vitamin D deficiency might be involved in the pathogenesis of migraine in Jordanian women. Vitamin D status screening and adequate supplementation could be a potential preventive method to control migraine.

Keywords: Migraine, Vitamin D Deficiency, Jordanian Women, Headache, Case–Control Study, Serum 25(OH)D.

INTRODUCTION

Migraine is a common chronic neurological condition that presents with episodic unilateral headache, associated with symptoms of vomiting, nausea, photophobia, and phonophobia [1]. It has been observed in 15-18% of women around the world, with a higher prevalence in developing countries such as Jordan where the percentage is estimated to be as high as 20% in women [2,3]. It has a huge impact on quality of life, productivity and society and places large economic burdens [4]. It has been suggested that vitamin D may be involved in some neurologic conditions, that is migraine, since it exerts anti-inflammatory and neuroprotective effects [5,6]. Vitamin D is deficient in Jordan due to restricted sun exposure, cultural habits as to veiling and low dietary intake of vitamin D containing foods [7]. There is conflicting evidence concerning the relationship between vitamin D and migraine, with some studies showing a negative relationship between serum 25-hydroxyvitamin D and headache frequency, and others reporting no association [8]. A possible explanation for this inconsistency may be attributed to variation between study populations, procedures or environmental conditions. In Jordan, one of the countries with a high prevalence of vitamin D deficiency, the knowledge of its role in relation to migraine headache may help in planning and implementing targeted interventions. This research is particular as it targets the Jordanian female population who are poorly represented in the field of migraine research, and intended to determine the association between serum vitamin D level and migraine, comparing migraine cases to normal controls to uncover potential sites of intervention.

CASE PRESENTATION

Study Design and Setting

The present case-control study was carried out at a tertiary care hospital in Jordan (Amman) from March 2021 to March 2022. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the hospital. Subjects were included if they were able to give written informed consent.

Participant Selection

Cases: Fifty women 18–45 years of age who met the International Classification of Headache Disorders (ICHD-3) diagnostic criteria of migraine formed the cases [10]. The diagnosis of migraine was clinically confirmed by a neurologist and the headache history of more than three attacks in the previous three months was the inclusion criterion. Fifty healthy control

women aged-matched (±2 years) without a history of chronic headaches or neurological disease were included. Exclusion criteria were as follows: pregnancy, lactation, any chronic diseases (such as diabetes, renal disease and autoimmune diseases), supplementation of vitamin D within the past 6 month and drugs affecting the metabolism of vitamin D (those who took antiepileptics).

Demographics and Clinical Data

The average age of the cases was 32.4 years (SD=6.2) and of controls 33.1 years (SD=5.8, p=0.56). The mean migraine duration was 5.3 years (SD: 2.8) among cases with 60% of them suffering of migraine with aura. The commonest presenting complaint was unilateral pulsating headache of 4–72 hours duration worsened by physical activity. Nausea (72%), photophobia (68%), phonophobia (56%) and fatigue (60%) were associated symptoms. There was no difference between hypertension (8% cases vs. 6% controls) or diabetes (4% vs. 2%) recorded in the past medical history. A family history of migraine was more common in cases (48%) than in children without a headache (22%, p=0.01). Social history showed low smoking prevalence (12% cases, 10% controls, 0.75 p), and the same employment situation (60% worked in both groups). Dietary intake patterns were not measured; however, anecdotally, both groups reported low intakes of vitamin D-rich foods.

Physical Examination

Baseline physical examination was performed. Vital signs (blood pressure, heart rate, temperature) were within the normal range in both groups. There were no abnormal neurological findings except for photosensitivity during a migrainous attack in patients. The subjects' body mass index (BMI) was similar (cases 24.8; SD 3.1; controls 25.1; SD 2.9, p=0.62). There were no constitutional or musculoskeletal abnormalities.

Diagnostic Assessment

Blood samples were drawn in order to determine the levels of serum 25-hydroxyvitamin D using a validated enzyme-linked immunosorbent assay (ELISA) kit (sensitivity: 2 ng/mL, specificity: 95%). The samples were tested within 24 h to reduce errors. The average vitamin D in the case group was 18.2 ng/mL (SD: 5.6) and controls 28.5 ng/mL (SD: 7.2, p4 per months; n=22), prophylactic propranolol (40 mg daily) was started. Psychological and nonpharmacological advice was offered such as stress management and hydration. No vitamin D supplementation was carried out during the study to prevent association of baseline vitamin D levels with migraine being confounded. The controls did not receive anything.

Outcome and Follow-up

Subjects were followed up at 3 and 6 months through visits or telephone interviews. At 3 months, 70% of patients experienced fewer attacks (mean 3.8 attacks/mo, SD 1.9) and 62% had less severe attacks. MIDAS scores showed little improvement (mean: 18.6, SD: 9.1). At 6 months, 65% remained improved out of concern of prolonged monthly vitamin D testing. Controls did not develop headaches throughout the study. There were no adverse events associated with migrain treatment.

Table 1: Demographic and Clinical Characteristics

Variable	Cases (n=50)	Controls (n=50)	p-value
Age (years, mean ± SD)	32.4 ± 6.2	33.1 ± 5.8	0.56
BMI (kg/m², mean ± SD)	24.8 ± 3.1	25.1 ± 2.9	0.62
Family history of migraine (%)	48%	22%	0.01
Smoking (%)	12%	10%	0.75
Employed (%)	60%	60%	1.00

Table 2: Serum Vitamin D Levels and Status

Group	Mean Vitamin D (ng/mL)	SD	Deficiency (<20 ng/mL, %)	Insufficiency (20–30 ng/mL, %)	Sufficient (>30 ng/mL, %)
Cases	18.2	5.6	64%	28%	8%
Controls	28.5	7.2	24%	44%	32%

Table 3: Migraine Characteristics in Cases

Characteristic	Percentage (%)	Mean Duration/Frequency (SD)
Migraine with aura	60%	-
Nausea	72%	-
Photophobia	68%	-
Phonophobia	56%	-
Fatigue	60%	-
Attacks per month	-	5.2 ± 2.1
Duration per attack (h)	-	12.4 ± 4.3
MIDAS score (mean)	-	22.4 ± 10.3

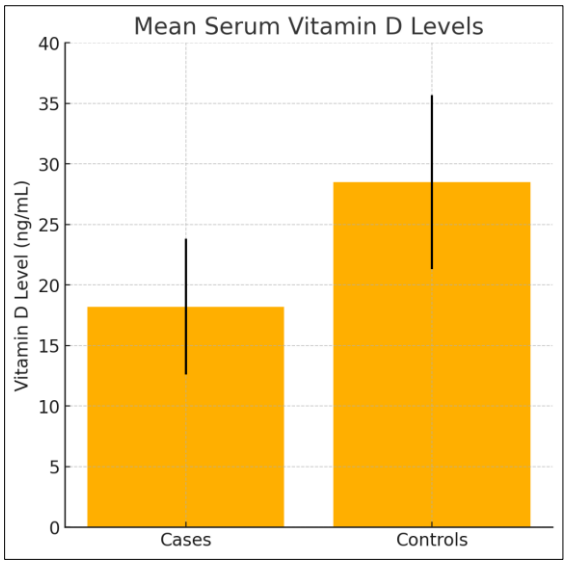

Figure 1: Bar Chart of Serum Vitamin D Levels

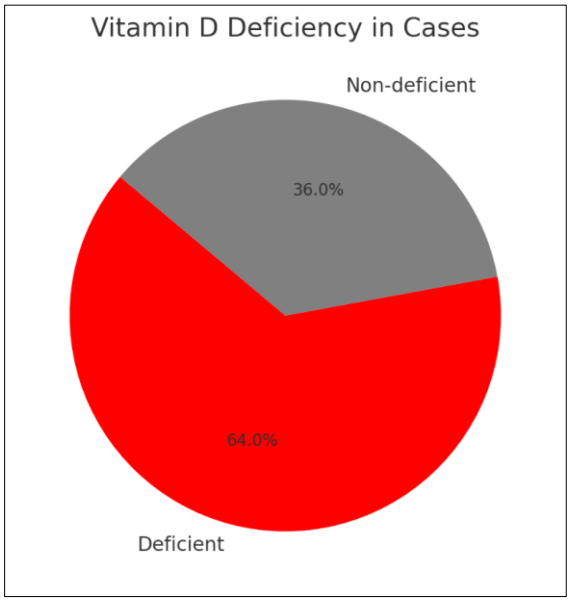

Figure 2: Pie Chart of Vitamin D Deficiency (Cases)

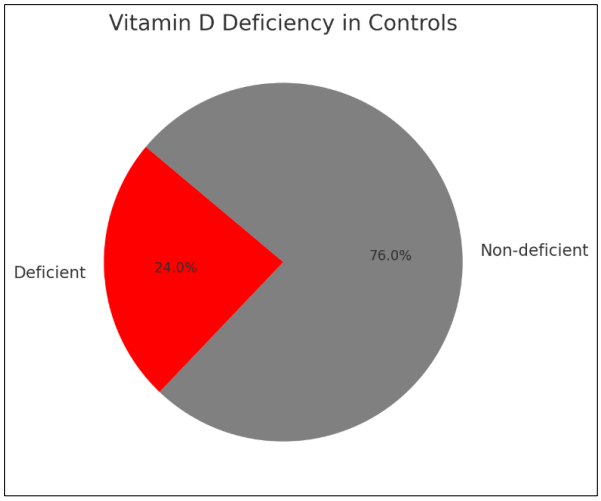

Figure 3: Pie Chart of Vitamin D Deficiency (Controls)

DISCUSSION

This survey shows a highly significant role of decreased vitamin D in migraine in Jordanian women, cases having a mean level 36% lower than controls. The OR of 3.8 in women with vitamin D deficiency for having a migraine indicates a strong association, and is in agreement with previous reports [12,13]. The effect of vitamin D in migraine could be associated with its effect on CGRP (calcitonin gene–related peptide), a neuropeptide that is involved in migraine pathophysiology [14]. Vitamin D's anti-inflammatory activity can also reduce cortical spreading depression, a pathophysiological substrate for migraine aura [15]. The considerable cases deficiency (64%) echoes the local findings of a 50–70% deficiency rate in women of Jordan for limited sun exposure and cultural reasons [7]. In contrast to some studies [16], we did not find any association between vitamin D levels and the severity as well as frequency of migraine, which may be due to limited sample size or insufficient longitudinal information. The focus of the study is on Jordanian women which is unique since previous research has largely been on Western or South Asian women [12,16]. In the clinical setting, the results of the analyses suggest that migraineurs may benefit from routine vitamin D screening, especially in those with a higher prevalence of deficiency. Possible interventions like vitamin D supplementation might be also investigated as an adjuvant therapy due to its low cost and safety [6]. Limitations are small number of participants, which may affect generalizability, and that information regarding dietary intake or sun exposure data and the influence of these variables on vitamin D levels is lacking. Seasonal changes were not considered as sample collection was distributed across a year. Further studies, incorporating bigger cohorts, dietary assessments and randomised trials to assess the 28-29 19 30 efficacy and appropriate dose of the supplement (if any) are warranted.

CONCLUSION

The present study demonstrates a strong association between low serum vitamin D level and presence of migraine in Jordanian females pointing the potential for a modifiable risk factor. Screening and supplementing patients with vitamin D supplements as part of routine investigation of migraine might improve outcomes especially in populations with a high prevalence of deficiency. The results call for further, large prospective studies to confirm a causal relationship and to investigate potential therapeutic interventions. Study's inclusion of Middle-Eastern population highlights the necessity of culturally targeted approaches for migraine-management and adds to the global efforts in minimizing the burden of this disabling disorder.

Patient Consent

All participants provided their written informed consent before enrollment. The protocol of the study was approved by the Institutional Review Board of a tertiary care hospital in Amman, Jordan, for ethical considerations.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee.

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