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ASSOCIATION BETWEEN VITAMIN D LEVELS AND CHRONIC MIGRAINE: A COMPARATIVE STUDY OF DIABETIC AND NON-DIABETIC PATIENTS USING ISI AND MIDAS SCALES.

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ABSTRACT

BACKGROUND: Insulin resistance, a pivotal factor in metabolic syndrome, has emerged as a recent link to migraine development. Limited research has explored the connection between migraine and diabetes mellitus. The potential role of metabolic syndrome in linking migraine, cardiovascular disease, and obesity underscores the need to investigate the relationship between migraine and low blood vitamin D levels. **OBJECTIVE:** to examine the association between vitamin d levels and chronic migraine: a comparative study of diabetic and non-diabetic patients using isi and midas scales. **METHODS:** This was a cross-sectional study was carried out from time march to September 2022. Participants that are migraine sufferers of both genders aged 20 to 50 years were included. The patients were divided into 2 groups: Group A included diabetic migraine patients and Group B included non-diabetic migraine patients. Vitamin D levels were observed for all patients including a detailed migraine history. The MIDAS (Migraine Disability Assessment) Test was be filled for assessment of patients. The ISI (insomnia severity index) was also taken which is 7-item self-report questionnaire that evaluates the nature, intensity, and effect of insomnia. Data was analyzed through SPSS version 23. **RESULTS:** In this study of 173 participants, comprising 91 males and 82 females, 37 were diabetic, and 136 were non-diabetic. The primary risk factors associated with migraine were excessive screen time, stress, tea intake, and food allergies. Significant differences were observed in the prodrome and attack phases of migraine between diabetic and non-diabetic groups. Pearson correlations revealed a negative association between Vitamin D levels and the Migraine Disability Assessment (MIDAS) score (r= -.617**, p=0.0496) and a positive correlation between Insomnia Severity Index (ISI) and MIDAS score (r= .717**, p=0.0316). These findings highlight the influence of diabetes on migraine symptoms and emphasize the role of Vitamin D levels and insomnia severity in migraine-related disability. **CONCLUSION:** Diabetes is associated with increased susceptibility to migraine prodrome and attack phases, while non-diabetic individuals are more likely to experience moderate sleep disturbances. Furthermore, our study revealed a modest negative link between vitamin D levels and migraine-related disability (MIDAS score), as well as a positive correlation between MIDAS score and insomnia severity.

KEYWORDS: Diabetes, ISI, Migraine, MIDAS, Vitamin D

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INTRODUCTION

Vitamin D is lipid-soluble vitamin that controls mineral homeostasis, maintains skeletal integrity, and governs cell development and differentiation. Vitamin D has 2 isoforms: the vitamin D2 (ergocalciferol) and the vitamin D3 (cholecalciferol). The vitamin D2 is received from diet and only supplies 10% of vitamin D needs, whereas the majority of vitamin D, around 90%, is generated through skin contact to sunshine.) Migraine is widespread and hindering brain illness, the mechanism of which is increasingly being studied. [2]

Migraine is a characteristic, as evidenced by neurophysiological information that grows and disappears in relation to attacks. The premonitory symptoms e.g., attention impairment, mood change, yawning, and homeostatic abnormalities including food and fluid imbalance precede the attacks, which might include more broad sensitivity such as photophobia and phonophobia. [3] Migraine is a common genetic chronic neurovascular illness marked by autonomic nervous system dysfunction. It has been associated with nausea and vomiting in certain individuals, as well as phonophobia, photophobia, and Osmophobia. [3] Migraine is critical and damaging brain illness ranked by the WHO as the 6th most incapacitating disease globally and most disturbing of all neurological diseases. Regrettably, its rating is rising with time. If both acute and chronic migraines are considered, it has a one-year prevalence of 15-18% globally. Migraine affects women three times more than men and has a considerable impact on quality of life, especially during peak productivity years. It is distinguished by episodes of unilateral and throbbing headache accompanied by sensitivity to visual, movement, auditory, as well as other afferent stimuli. Additional symptoms including weariness, irritation, decreased focus, and yawning might occur up to 48 hours before the headache: premonitory phase. Majority of episodes are observed by hours or days of feeling ill, generally with fatigue, known as postdrome. Furthermore, roughly one-third of migraine sufferers have neurological impairments, including cortical disturbances, which are referred to as migraine aura. [4] Several studies have found that vitamin D is beneficial to musculoskeletal health across a wide range of activities. Vit-D works as a developmental neuroactive steroid, regulating numerous nervous system processes and neurotransmitter levels. Motaghi et colleagues discovered that polymorphisms in vitamin D receptor (VDR) gene may enhance likelihood of having migraine with no aura. [5] It is uncertain what function vitamin D deficiency plays in headaches. The major processes generating headaches include probable sensitization of 2nd and 3rd neurons owing to persistent excitation of periosteal sensory receptors (due to bone enlargement) and central sensitization (due to bone swelling).[6] In research done in Peshawar, Pakistan, the prevalence of migraine caused by vitamin D insufficiency was reported to be 15%. [(7)] Migraine treatment with vitamin D increased neuromuscular function in hypovitaminosis patients by expanding the cross-sectional region of type IIA fast-twitch fibers and boosting strength of proximal muscles.[7] Vitamin D supplementation has been shown to reduce inflammatory indicators such as C-reactive protein (CRP), which can lower neurogenic inflammation in migraine development. [8] VTD appears to be significant in the islet cell death prevention and may be effective in advancing the survival of islet cell transplants. Vitamin D is necessary for and enhances insulin production, as well as insulin sensitivity [9] discovered that those with migraine were more likely to develop diabetes than people who did not have migraine.[9] Insulin resistance, which is essential in etiology of metabolic syndrome, has recently been linked with migraine development. [9]

Limited research has explored the connection between migraine and diabetes mellitus. A

study involving 1450 senior Brazilians found no statistically significant link between diabetes and migraine, although it didn't account for migraine subtypes. Another study, which didn't differentiate migraine subtypes, also found no association between migraine and diabetes.[10] However, the link between obesity, migraine, and increased cardiovascular disease may be explained by metabolic syndrome, which includes insulin resistance. Migraine sufferers have shown poorer insulin sensitivity in various studies. Investigating the relationship between migraine and low blood vitamin D levels is crucial and may benefit both migraine sufferers and society in the long term.

MATERIALS AND METHODS

This was a cross-sectional study, carried out at Department of Physiology, LUMHS Jamshoro. The study was performed for of 6 months e.g., March 2022 to September 2022. Study subjects were diagnosed migraine patients, in which two groups were formed Group A comprised of Diabetic Migraine Patients and Group B comprised of Nondiabetic Migraine patients. Patient aged 20 - 50 years, diagnosed cases of migraine and Diabetic patients with migraine were selected for this study. Patients with other neuromuscular disorders or taking vitamin D supplements or Epileptic patients or having any metabolic disorders other than mentioned were excluded from the study. Study was carried out after the approval from ERC of Liaquat University of Medical and Health Sciences Jamshoro. An informal consent was taken from participants prior filling the questionnaire. Those who refused to participate in study or did not fully comprehend study's aims or outcomes were interviewed. A blood sample was collected for the screening of vitamin D levels at Diagnostic Lab Jamshoro/Hyderabad. Vitamin D test was done on Cobas e411 machine through COBAS microplate assay. Patients were categorized into two groups. A detailed history of the diagnosed patient of migraine was taken. And MIDAS questionnaire was filled for assessment of patient. The ISI (insomnia severity index) is 7-item self-report questionnaire that assesses the nature, intensity, and impact of insomnia.

The statistical analysis was made by SPSS 23.0. The mean and standard deviation were assessed for quantitative variable. Frequency and percentages were assessed for categorical parameters. Statistical correlation was conducted through a non-parametric correlation test: Kendall's tau test for relationship between levels of vitamin D and MIDAS grades in both groups (Diabetic & Non-Diabetic). Statistical correlation was conducted through a non-parametric correlation test: Kendall's tau test for the association between MIDAS and ISI scores in both groups (Diabetic & Non-Diabetic). Both groups were compared. P value of <0.05 was taken as statistically significant.

RESULTS

This cross-sectional analysis conducted on 173 population size, out of which 91 (52.6%) were male and 82 (47.39%) were female diagnosed cases of migraine **(Table 1)**. Out of which 37 (21.38%) were diabetic and 136 (78.61%) were non-diabetic control group **(Table 2)**. Urban population has 2:1 higher probability of acquiring migraine as compared to rural population **(Table 2)**. Most common risk factors for developing migraine were found out to be excessive screen time, stress, tea intake and food allergies **(Table 3)**. There was significant difference of prodrome and attack phase of migraine between group A (diabetic) and group B (Non-diabetic) **(Figure 1)** with p value <0.05 and there is also significant difference of grading of Insomnia among both groups, as most frequent were mild insomnia with 37% and 47% respectively **(Figure 2)**. Pearson correlations were applied between Vitamin D levels and MIDAS score, were found out to be ($r= -.617$) with ($p=0.04$) which signifies there is moderately negative correlation between both variables and their interdependency **(Table 4-5)**. Pearson correlations were applied between ISI (Insomnia severity index) and MIDAS score, were found out to be ($r= .717$) with ($p=0.03$) which signifies there is positive correlation between both variables and their interdependency **(Table 6-7)**. ANOVA test was applied and Vitamin D levels, MIDAS score, ISI score and screen time, and values were found out to be significant with P values of <0.001 **(Table 8)**.

Table 1: Demographics Data of Patients (n=173)

Gender	Frequency (Percentage)	Age (mean) in years	BMI (mean) In kg/m²	Urban	Rural
Male	91 (52.6%)	31.32	34.9	51 (29.47%)	18 (10.40%)
Female	82 (47.39%)	33.19	36.13	67 (38.7%)	37 (21.48%)

Table 2: Distribution of Migraine among Groups (n=173)

Diagnosis	Frequency	Percentage	Male	Female	P value
Group A (Diabetic)	37	21.38%	15 (40.5 %)	22 (59.45 %)	0.0357
Group B (Non-diabetic)	136	78.61%	54 (39.7 %)	82 (60.29 %)	

Table 3: History and Risk Factors for Migraine (n=173)

Factors	Group-A (Male) n= 15		Group-A (Female) n= 22		Group-B (Male) n= 54		Group-B (Female) n= 82	
Responses	*Yes (%)*	*No (%)*	*Yes (%)*	*No (%)*	*Yes (%)*	*No (%)*	*Yes (%)*	*No (%)*
Family History	13	87	21	79	17	83	31	69
Smoking Status	37	63	13	87	33	67	37	63
Marital Status	45	55	35	65	41	59	41	59
Physical Inactivity	57	43	37	63	64	36	67	33
Healthy diet status	21	79	31	69	22	78	31	69
Central Obesity	69	31	59	41	61	39	59	41
Tea/ Coffee intake	82	18	73	27	81	19	78	22
Family stress	71	29	89	11	75	25	81	19
Work stress	71	29	89	11	77	23	87	13
Excessive screen time	87	13	89	11	91	09	91	09
Food allergy	13	87	15	85	17	23	19	81

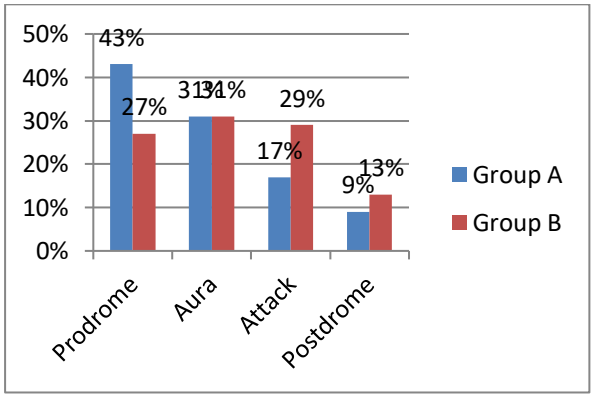

Figure 1: Phases of Migraine among Groups (n=173)

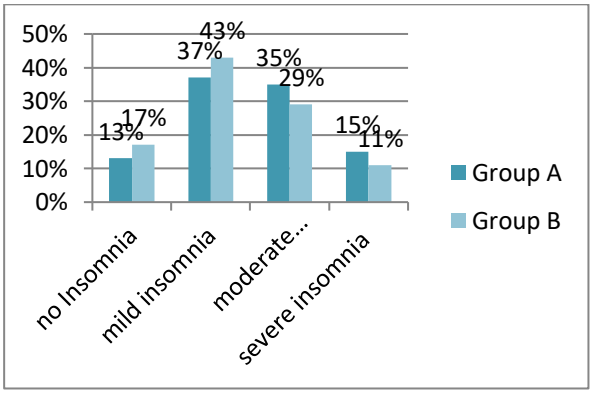

Figure 2: Severity of Insomnia among Groups (n=173)

Table 4: Vitamin d and MIDAS score (n=173)

Variables		MIDAS Score
Serum Vitamin D	*R-value*	-.617
	p-value	0.0496

Table 5: One Sample T-test for Vitamin D and MIDAS Score (n=173)

Variables	Mean	Std Deviation	Standard error mean	T	P
Serum Vitamin D	12.946	9.7903	.9992	12.956	0.04
Midas Score	31.48	9.316	1.155	27.257	

Table 6: Insomnia and MIDAS Score (n=173)

Variables		Midas Score
ISI Score	R-value	.717
	p-value	0.0316

Table 7: One Sample T-test for Insomnia and MIDAS Score (n=173)

Variables	Mean	Std Deviation	Standard error mean	T	P
ISI Score	15.751	4.624	.8332	31.812	0.03
Midas Score	31.48	9.316	1.155	27.257	

Table 8: Comparison of Variables between Groups (n=173)

		Sum of Squares	df	Mean Square	F	Sig.
Vitamin D levels	Between Groups	2297.783	23	99.904	4.199	.0001
	Within Groups	1713.176	72	23.794		
	Total	4010.958	95			
Midas Score	Between Groups	2918.161	23	126.877	6.256	.0001
	Within Groups	1460.329	72	20.282		
	Total	4378.490	95			
ISI score	Between Groups	11181.507	23	486.152	35.628	.0001
	Within Groups	982.451	72	13.645		
	Total	12163.958	95			
Screen time	Between Groups	68281.941	23	2968.780	5.364	.0001
	Within Groups	39847.017	72	553.431		
	Total	108128.958	95			

DISCUSSION

This study emphasizes the findings of previous studies by demonstrating a positive association between vitamin D levels and MIDAS (Migraine disability assessment) SCORE and ISI (Insomnia severity index) scores. This association was found even after confounding variables were controlled, i.e., age, sex, body mass index, circumference of waist, education level of, and the presence of multiple chronic conditions. However, there has been negative correlation seen between blood vitamin D levels and migraine severity. Within the scope of current study, we also investigated the possible correlation between migraines and various amounts of vitamin D. Some studies suggest that vitamin D has a very useful role in headache, including migraine[11-13]. 2 patients having migraine and PMS/menstruation were studied in this case report research. Patients with low vitamin D levels saw a decline in attacks of migraine and premenstrual symptoms after two months of therapy with a combination of calcium and vitamin D supplements (1600-1200 IU/day) [12,13]. A separate study conducted on post - menopausal clients having migraine and decreased levels of vitamin D found that consumption with calcium and vitamin D reduced the incidence as well as severity of migraine episodes[12]. Parkash et al. found that after 4-6 weeks of using a calcium and vitamin D supplement (1500 IU vitamin D3 and 1000 mg calcium), he observed a reduction in headache severity in eight individuals having vitamin D insufficiency, osteomalacia, as well as persistent tension-type headache. Serum calcium levels normalized after one week of therapy, but headache symptoms improved after many weeks; therefore, vitamin D is likely much significant than calcium in relieving headache symptoms[(11)]. Kjćrgaard et al. and Knutsen et al. suggested that poor vitamin D levels are associated with increased prevalence of chronic discomfort and headache[14,15]. Turner *et al* have reported the 26% of more than 250 individuals with persistent pain had vitamin D insufficiency including 25 patients with headache[16]. Atherton et al. have shown that women in England were found to have a

stronger correlation between vitamin D levels and chronic pain than males were[18]. Hypovitaminosis D was observed in 58% patients with headache, pain in musculoskeletal region, and exhaustion in multi-racial research using descriptive and cross-sectional study designs conducted in Norway. There was negative association between headache and vitamin D levels, and higher vitamin D levels were associated with fewer headache bouts, even after controlling for gender, age, season, and geographic location (OR = 2.6, P = 0.008). Patients experiencing headaches also had lower vitamin D serum levels than those without headaches. Winter and spring have lower vitamin D levels than summer and fall[17]. another study showed that deficiency of vitamin D is common among migraine sufferers[19,20]. Furthermore, Wheeler et al. stated that 14.8% patients having chronic history of migraine had blood vitamin D levels that were ≤20 ng/ml, whereas 25.9% patients had levels of vitamin D that ranged from 20-30 ng/ml[19]. With adjustments made for age, body mass index, gender, season, chronic illnesses, level of education, physical action, and drinking habits, a cross-sectional research involving more than 11,000 respondents in the 6th survey of Troms study found highly strong relation among non-migraine pain and vitamin D levels in non - smoker[14]. Precise role of vitamin D deficiency among patients with headache is not known but Prakash et al. have shown that constant stimulation of periosteal covering sensory receptors (owing to bone swelling) may be the primary mechanism behind headaches, although cerebral sensitization may also play a role (because of bone swelling). Low blood magnesium levels are another potential explanation of headache among persons with insufficiency of vitamin D. Also, abnormal magnesium metabolism is implicated in pathophysiology of tension-type headache. Patients suffering from tension headaches and other forms of headache often have magnesium deficit in their brain, blood, erythrocytes, monocytes, and platelets. Serum magnesium levels are decreased in around 40-50% of those with tension-type headache. Such patients have shown improvement when treated with magnesium in many studies[11]. Since vitamin D is required for intestinal absorption of magnesium via food, deficiency of vitamin D may contribute to tension-type headache through reduced magnesium absorption[21]. A Previous study has addressed how migraine might cause youngsters to have trouble sleeping. Disorders of beginning and sustaining sleep were more common among children with migraine (37.1% vs. 9.2% in controls), whereas the incidence of awakening disorders was increased among children with migraine (59.3% vs. 10.2% in controls) than among children without headaches[1)]. Dosi et al have shown that possible precursors to adult headache include infant sleep problems[20]. Sauro et al. have shown that subjects with migraine and sleeplessness had a greater incidence of headaches and a higher HIT-6 score than those who did not suffer from insomnia.[21] Results suggest that insomnia is linked to the chronification of migraine and PM, which makes sense given that frequent headaches are a risk factor for chronification. Insomnia was also related with a higher HIT-6 score among those who suffered from migraines and PM. This finding may suggest that insomnia contributes to the prevalence of migraine and PM.[22]

CONCLUSION

Diabetes is associated with an increased risk of migraine prodrome and attack phases, while non-diabetic individuals experience more moderate sleep disturbances. Vitamin D levels show a negative correlation with Migraine Disability Assessment Scale (MIDAS) scores, while the Insomnia Severity Index correlates positively with MIDAS scores. Common migraine triggers include excessive electronic device use, stress, caffeine consumption, and food allergies. These findings emphasize the potential importance of maintaining adequate vitamin D levels in managing migraines, especially in individuals with diabetes

ETHICS APPROVAL: The ERC gave ethical review approval

CONSENT TO PARTICIPATE: written and verbal consent was taken from subjects and next of kin

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