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Original Article

Relationship of serum Vitamin D levels to the severity of tension-type headache

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ABSTRACT

Conflicting reports exist on the association between the severity of tension-type headache (TTH) and serum Vitamin D levels. This study aimed to determine the relationship between serum Vitamin D levels and headache severity among persons with TTH in our locality. Using a cross-sectional analytical study design, eligible adult patients with TTH were consecutively recruited at the neurology clinic of the Lagos University Teaching Hospital, Nigeria. Their age and sex matched healthy headache-free controls were also recruited. Demographic information and clinical parameters were obtained with an interviewer-administered questionnaire. Headache severity and pain intensity were documented using the incorporated headache disability index (HDI) and numerical rating scale (NRS) tools, respectively. Serum levels of Vitamin D, calcium, and albumin were assayed for all study participants. The study recruited 65 persons with TTH and 50 control subjects. The TTH subjects comprised 20 males and 45 females, with mean ages of 34.4 ± 13.1 and 33.4 ± 10.8, respectively. The mean serum Vitamin D level among the participants was 55.8 g/mL ± 28.1. The mean NRS among participants was 6.2 ± 1.49, while the mean HDI among participants was 27.3 ± 19.6. There was no correlation between serum Vitamin D levels and the severity of TTH. We found no relationship between serum Vitamin D level and headache severity or pain intensity in TTH.

Keywords: Headache, Intensity, Severity, Tension-type headache, Vitamin D

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INTRODUCTION

Population studies show a significant decrease in the national gross domestic product linked to primary headache disabilities.[1] Tension-type headache (TTH) is regarded to be the most common primary headache.[2] The prevalence and severity of TTH differ widely between countries, and there is an intriguing geographic pattern. Some studies on the seasonal variation of TTH report an increased frequency of headache attacks in autumn/winter and the fewest attacks in summer, which matches the seasonal variations of serum Vitamin D levels.[3] Although studies have suggested some relationship between serum Vitamin D levels and frequency of TTH, the role of serum Vitamin D level in TTH intensity and severity remains unclear.[4]

The name TTH implies that pain is a product of nervous tension, but there is no clear evidence for tension as an etiology.[5] The supposition that the pain is muscular in origin and related to increased resting muscle tension corresponds with the current clinical understanding of TTH and derived treatment approaches.[5] Reports indicate that administering Vitamin D supplements decreases pain score in persons with chronic pain, and Vitamin D influences the relief of musculoskeletal pain; an effect speculated to be a consequence of decreasing the sensitivity of nerve fibers in the muscles.[6] Vitamin D deficiency enhances the sensitization of second

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and third-order neurons associated with sensory receptors in periosteal covering and central sensitization.[7]

TTH is reportedly highly prevalent in Nigeria.[8] To clarify how the mixed reports about serum Vitamin D levels and headache severity apply to our local setting, we assessed serum Vitamin D levels in persons who presented with TTH at a tertiary health facility in Lagos, Nigeria. Our study aims to investigate the association between serum Vitamin D levels and headache severity in patients with TTH. The study hypothesis was that no association exists between serum Vitamin D level and headache severity in TTH.

MATERIALS AND METHODS

This cross-sectional analytical study was carried out at the Lagos University Teaching Hospital (LUTH) located in the city of Lagos, Nigeria.

Study Population

Persons diagnosed with TTH who met the eligibility criteria were recruited consecutively at the hospital.

Inclusion Criteria

Adults (age 18 years and above) who fulfilled the International Classification of Headache Disorders (ICHD) 3 diagnostic criteria for TTH.

Exclusion Criteria

Patients with headache disorders other than TTH, pregnancy, clinical evidence of chronic kidney disease or chronic liver disease, and those on medications that could affect serum Vitamin D level, such as phenytoin, carbamazepine, phenobarbital, rifampicin, glucocorticoids, highly active anti-retroviral therapy, and regular Vitamin D supplementation.

Control Recruitment

Healthy consenting subjects with no history of headache disorder who were age- and sex-matched with the TTH patients were recruited for the study to determine a population-appropriate reference range value for Vitamin D.

Data Collection

This study was conducted over 1 year. A well-structured standard pro forma was administered to each participant to document demographic data, clinical characteristics of the headache, headache frequency, and severity. Physical examination, including general physical examination, anthropometric measurements, and neurological examination, was performed on all study participants. A diagnosis of TTH was made according to ICHD-3 diagnostic criteria. The severity of headache was assessed using the headache disability index (HDI), whereas the intensity of headache was assessed using the numerical rating scale (NRS).

Vitamin D Estimation

A sterile syringe was used to collect venous blood (5 mLs) in a plain sterile container transported in a cold chain to the research laboratory of the College of Medicine, Idi-Araba, Lagos, and was centrifuged at 3000 rev/min for 10 min within 2 h of collection. Serum was obtained from the centrifuged sample and stored at a temperature of −20°C. During analysis, thawed samples were allowed to equilibrate to room temperature for at least 30 min and were mixed before batched analysis using the Enzyme-Linked Immunosorbent Assay (ELISA) method.

Samples were analyzed for serum Vitamin D levels using an ELISA kit from Calbiotech according to the manufacturer's instructions. Serum calcium and albumin were run by automation using the Roche Cobas C311 automated chemistry analyzer. The corrected serum level of calcium was calculated after determining the serum level of total calcium and albumin.

Operational/Case Definitions

Diagnosis of TTH was defined based on ICHD-3 diagnostic criteria. HDI score was interpreted as follows: ≤28% Mild disability, 30–48% Moderate disability, 50–68% Severe disability, and ≥70% Complete disability. Serum Vitamin D levels were defined as low, normal, and high for any values below the 1st quartile, between the 1st and 3rd quartile and above the 3rd quartile of the serum Vitamin D levels of controls, respectively.

Data Management

Data were stored electronically using a Microsoft Excel spreadsheet and subsequently analyzed with the IBM Statistical Package for the Social Sciences (SPSS®) version 21.0 (IBM Corp., Armonk, NY, USA).

Continuous variables were presented as means and standard deviation (SD), whereas categorical variables were presented as frequency and proportions. Student's *t*-test was used to compare the means of numerical variables, and analysis of variance was employed when the groups were more than two. Non-parametric tests such as median, interquartile range, Kruskal–Wallis test, and Mann–Whitney U-test were used for data that were not normally distributed.

Chi-square test was used to test for the association between two or more groups of categorical variables. Correlation analysis was used to explore the relationship of serum Vitamin D level to NRS and HDI.

Multivariate regression analysis was used to explore the predictive relationship of serum Vitamin D levels to headache severity while controlling for the influence of some selected clinical variables (age, sex, age at onset, body mass index [BMI], duration of headache, frequency of headaches, exposure to sunlight, and use of preventive medications). $P < 0.05$ was considered statistically significant.

RESULTS

Sixty-five patients with TTH fulfilled the stipulated inclusion criteria for the study, while 50 control subjects participated in the study. There was no statistically significant difference between the age and sex distributions of the TTH patients and control subjects.

Among the participants, twenty subjects were male with their ages ranging from 19 to 65 years and a mean age of 34.4 ± 13.1 years, while 45 subjects were female within the ages of 18–61 years and a mean age of 33.4 ± 10.8 ($P = 0.74$). Other details of the TTH subjects, including the age at onset, body mass index, and daily outdoor exposure to sunlight, are shown in Table 1. The male and female subjects showed no statistically significant difference in clinical and anthropometric features.

The median, mean ± SD serum Vitamin D levels among TTH patients and control subjects were 50.1 ng/mL, 55.8 ng/mL ± 28.1, and 44.6 ng/mL, 48.8 ng/mL ± 23.33, respectively ($P = 0.19$). The 1st and 3rd quartiles of the serum Vitamin D levels of the controls, indicating the derived cutoff points for low and high levels of Vitamin D, were 32.8 ng/mL and 58.5 ng/mL, respectively. Serum Vitamin D levels of 32.8 ng/mL −58.5 ng/mL constituted between the 1st and 3rd quartiles of the values in the control subjects, interpreted as normal values [Table 2].

The comparison of headache severity and intensity between TTH patients with low, normal, and high serum Vitamin D levels yielded no difference across the groups, as shown in Table 3. Using Spearman's correlation, there was no significant correlation between headache severity or intensity and serum Vitamin D levels among the TTH subjects ($r_s = -0.138$; $P = 0.272$ and $r_s = 0.072$; $P = 0.567$, respectively).

Multivariate analysis, using linear regression, yielded no predictive relationship of serum Vitamin D level with HDI score and pain intensity while controlling for some selected variables (age, sex, age at onset, BMI, duration of headache, frequency of headaches, and duration of exposure to sunlight) as shown in Table 4. A shorter duration of outdoor exposure to the sun was an independent predictor of headache disability index among the participants with TTH.

Dependent variables: Headache disability index (HDI) and numerical rating scale (NRS)

Table 4 shows that a shorter duration of outdoor exposure to sun is an independent predictor of headache disability index among the participants with tension-type headache.

DISCUSSION

TTH appears to be most burdensome between the ages of 15 and 49 years.[2] The majority of the patients in this study were within this age range. The overall mean age of the TTH cases in this study (33.7 ± 11.4) is close to reports from a previous study by Oshinaike *et al*. at a tertiary health center. In addition, the mean age of onset for TTH in this study mirrors the report by Oshinaike *et al*. (30.5 ± 10.8 years).[8] In this study, there were more females than males among TTH patients. Ojini *et al*. and Wahab and Ugheoke, who worked in some other parts of Nigeria, reported some pattern of female preponderance, though the extent of female preponderance observed in this study appears higher than reported by these studies.[9,10] The variations from the levels of female preponderance reported in this study may reflect differences in health-seeking behavior across sexes, since this is a hospital-based study.[11] Anthropometric parameters, such as weight and BMI, have been used to enumerate fatness or adiposity, and BMI is recognized as a predictor of Vitamin D levels.[12] The mean value of BMI among the study participants was like the mean BMI value (24.8 ±4.9 kg/m^2) reported among a Lagos population of a similar age range; in the study by Sonuyi *et al*.[13] This study did not observe any association between BMI and TTH, in keeping with previous studies.[14]

The role of Vitamin D in TTHs and several other diseases has been a subject of recent interest to researchers.[3-5] Understanding the clinical profile and comorbidities can add important new insights into the pathophysiology and the optimal therapy of TTH.

A few observations suggest a link between low serum Vitamin D levels and a higher incidence of chronic pain.[15] This study did not show a remarkable difference in serum Vitamin D levels between TTH cases and controls. In contrast, a study by Prakash *et al*. among persons with TTH showed a mean serum Vitamin D concentration of 15 ng/mL compared to 27 ng/mL in the controls, implying a lower serum Vitamin D concentration in TTH patients compared to controls.[4] Differences in the study designs could have influenced the variation in study outcomes, as the study by Prakash *et al*. recruited only patients with chronic TTHs.[4]

Certain tools have been available in recent years to assess the severity of problems associated with headaches, including patient case reports.[16] Quantification of the disability in headache patients is of great importance in determining the severity of the disease and guiding the approach to management.[17] The headache disability index and the pain NRSs were used to assess the severity of headaches among participants in this study.[17]

The study did not show a relationship between the intensity of headache (using NRS) and serum Vitamin D level among

Table 1: Clinical and anthropometric features of participants with TTH

Parameter	Male (*n*=20)	Female (*n*=45)	Total (*n*=65)	Statistic	*P* value
Age at onset (in years)				*t*-test	
Range	15–60	15–46	15–60		
Mean (SD)	34.6 (12.2)	28.7 (9.8)	30.5 (10.8)	1.92	0.06
BMI (Kg/m^2)				*t*-test	
Range	16.7–31.5	17.9–39.8	16.7–39.8		
Mean (SD)	25.0 (3.8)	25.5 (4.7)	25.4 (4.4)	0.45	0.66
BMI category				χ^2	
<18.5 (%)	1 (5)	1 (2.2)	2 (3.1)		
18.5 to 24.9 (%)	9 (45)	23 (51.1)	32 (49.2)		
25 to 29.9 (%)	8 (40)	14 (31.1)	22 (33.8)		
≥30 (%)	2 (10)	7 (15.6)	9 (13.8)	1.42	0.75
Daily outdoor exposure to sun (in hours)				*t*-test	
Range	1–12	1–9	1–12		
Mean (SD)	4.15 (3.3)	4.1 (2.4)	4.1 (2.7)	0.08	0.94
Median	3.0	4.0	3		
Headache severity using HDI				*t*-test	
Range	8–78	0–70	0–78		
Mean (SD)	30.5 (19.5)	25.8 (19.7)	27.3 (19.6)	0.90	0.38
Median	26.0	20.0	22		
Interquartile range	14–40	8–44	12–41		
Categories of HDI				χ^2	
Mild (%)	11 (55)	30 (66.7)	2 (3.1)		
Moderate (%)	6 (30)	6 (13.3)	41 (63.1)		
Severe (%)	2 (10)	8 (17.8)	12 (18.5)		
Complete (%)	1 (5)	1 (2.2)	10 (15.4)	3.47	0.30
Pain intensity using NRS				*t*-test	
Range	3–9	3–8	3–9		
Mean (SD)	6.2 (1.79)	6.2 (1.36)	6.2 (1.49)	0.01	0.99
Median	6	6	6		
Interquartile range	5–8	5–7	5–7.5		

%: Percentage; SD: Standard deviation, χ^2: Fisher's exact test, BMI: Body mass index, HDI: Headache disability index, NRS: Numerical rating scale

participants who presented with TTH. This is reminiscent of the findings from a similar study about Vitamin D levels in migraine.[18] Similar studies had linked serum Vitamin D deficiency to increased frequency of headaches in TTH rather than severity of headache, which was the focus of this study; for instance, Prakash *et al*. observed more frequent headaches in TTH patients with lower serum Vitamin D levels, whereas Knutsen *et al*. reported that supplementing serum Vitamin D did not affect headache and pain scores despite improving serum Vitamin D levels.[4,19] Regarding the headache disability index, this study did not establish a correlation with serum level of Vitamin D. Indeed, the results suggest a similar Vitamin D status across the various categories of headache disability.

The self-reported daily duration of exposure to sunlight was the only clinical variable seen to be a predictor of headache severity in patients who presented with TTH. A shorter duration of exposure to sunlight was an independent predictor of headache disability index in TTH. Exposure to ultraviolet radiation from the sun promotes the synthesis of Vitamin D from a precursor in the skin.[20] A study reported that an average daily sun exposure of 1–2 h was required in a tropical region to maintain serum Vitamin D levels above 50–100 nmol/L, respectively.[21] Although exposure to sunlight is known to impact serum levels of Vitamin D,[20] it is noteworthy that the predictive relationship of exposure to sunlight with headache severity noted in this study did not extend to serum Vitamin D levels. This is unsurprising, considering that the

mean duration of sunlight exposure for the participants in this study (4.1 ± 2.7 h) exceeded the one to 2 h needed to induce an increase in Vitamin D level in the tropics, as reported by Vivek *et al*.[21] The predictive relationship between exposure to sunlight and headache severity shown in this study could be because of the adopted sick role; people are more likely to stay indoors in the event of an ailment becoming more severe.

Table 2: Biochemical profile of TTH and control subjects

Parameter	TTH (*n*=65)	Control (*n*=50)	Statistic	*P* value
Serum Vitamin D level (ng/mL)			U	
Range	27.5–152.2	8.9–126.2		
Mean (SD)	55.8 (28.1)	48.8 (23.33)		
Median	50.1	44.6		
Interquartile range	33.5–64.2	32.8–58.5	1394.5	0.19
Serum calcium level (mmol/L)			*t*-test	
Range	0.91–2.24	1.12–2.23		
Mean (SD)	1.82 (0.33)	1.91 (0.30)	1.50	0.14
Serum albumin level (g/L)				
Range	33.7–52.4	38.2–53.8		
Mean (SD)	44.4 (3.95)	45.5 (3.82)	1.46	0.15
Corrected serum calcium (mmol/L)				
Range	0.80–2.38	1.10–2.49		
Mean (SD)	1.91 (0.38)	2.02 (0.35)	1.61	0.11

SD: Standard deviation, U: Mann–Whitney U-test, TTH: Tension-type headache

Contrary to the case with exposure to sunlight, our multivariate analysis exploring the possible predictive relationship of serum Vitamin D levels to headache severity while controlling for the influence of some clinical variables showed no relationship between the severity of TTH in the participants and their age, sex, and BMI. The lack of direct influence on TTH severity by age in this study may not be very distinct from the experience of Palacios-Ceña *et al*., who barely found a weak correlation between the age of patients and the extent of pain in those with TTHs among a Spanish population.[22] Should such an association exist, perhaps the index study could not detect the same because of some differences in the characteristics of the study participants. For instance, their study focused on middle-aged participants, whereas the bulk of the patients in this study clustered around the young adults to middle-aged group, with poor representation of older adults.[22] Non-existence of a predictive relationship of headache severity with the sexes of participants corroborates the observations of Rollnik *et al*., who reported no difference in pain intensity and frequency of headaches between males and females with TTHs.[23] We did not find BMI to be a predictor of headache severity, in tandem with the study by Bigal *et al*., which failed to establish obesity as an exacerbating factor for other types of headaches besides episodic migraine.[24] Furthermore, a large population study that demonstrated an association between obesity and Chronic Daily Headaches opined that it is relatively specific for chronic migraine rather than TTHs.[25]

Table 3: Headache severity across categories of serum Vitamin D level among participants with TTH

Parameter	Low serum Vitamin D level (*n*=12)	Normal serum Vitamin D level (*n*=31)	High serum Vitamin D level (*n*=22)	Statistic	*P* value
HDI				K-W	
Range	6–64	0–78	6–64		
Mean (SD)	30.2 (17.9)	25.2 (21.7)	28.6 (17.8)		
Median	29	18	22		
Interquartile range	19–39	8–42	17–48.5	1.73	0.42
HDI category				χ^2	
Mild (%)	6 (50.0)	22 (71.0)	13 (59.1)		
Moderate (%)	4 (33.3)	4 (12.9)	4 (18.2)		
Severe (%)	2 (41.7)	3 (9.7)	5 (22.7)		
Complete (%)	0 (0)	2 (6.5)	0 (0)	5.62	0.45
NRS				K-W	
Range	3–9	3–8	4–8		
Mean (SD)	6.0 (2.0)	6.0 (1.5)	6.5 (1.2)		
Median	5.5	6.0	6.5		
Interquartile range	4.3–8	5–7	5.8–7.3	1.17	0.56

%: Percentage, SD: Standard deviation, χ^2: Fisher's exact test, K-W: Kruskal–Wallis test, HDI: Headache disability index, NRS: Numerical rating scale

Table 4: Predictive relationship of serum Vitamin D level to headache severity and pain intensity, with control for the influence of some selected variables

Determinants	Headache severity			Pain intensity		
	β-coefficient	t	*P*-value	β-coefficient	t	*P*-value
(Constant)	46.33	2.446	0.018	4.539	2.875	0.006
Sex	0.157	1.219	0.288	0.063	0.451	0.654
Age	0.184	1.465	0.149	0.263	1.917	0.060
Age at onset	−0.123	−1.821	0.415	−0.122	-0.746	0.459
Body mass index	−0.168	−1.300	0.199	0.063	0.443	0.659
Duration of exposure to sun	−0.260	−2.042	**0.046**	−0.155	−1.113	0.271
Duration of headache	−0.093	-0.733	0.467	0.159	−1.145	0.257
Frequency of headache	0.237	1.923	0.060	0.037	0.277	0.783
Use of preventive drugs	−0.103	−0.780	0.439	0.081	0.559	0.578
Serum Vitamin D level	−0.073	−0.558	0.579	0.132	0.920	0.362

Bold value denotes shorter duration of exposure to sunlight predicted increased headache severity

Similarly, the duration and frequency of headaches were not predictive, unlike in the studies by Gopichandran *et al*. and Schwart *et al*., respectively.[26,27] Although the study by Schwart *et al*. linked Chronic TTH to more lost workdays and reduced effectiveness days compared with subjects with Episodic TTH, this did not translate to higher severity of headaches among patients with Chronic TTH.[27] Preventive medication usage in TTH has shown modest effectiveness over the years and would usually require additional nonpharmacological therapy.[28] In this study, the use of preventive medications was not a predictor of headache severity and, therefore, was not expected to be a confounding factor.

Limitations

We used ELISA to assay for Vitamin D, whereas the high-performance liquid chromatography method is considered the gold standard assay for Vitamin D. Our decision to exclude prospective subjects who had recently taken Vitamin D supplements or include prospective subjects who did not take Vitamin D supplements was based on the subjects' self-reports, this could have been affected by recall bias. Data collection, including laboratory sample collection for Vitamin D assay, spanned 1 year across different seasons, and sample collection was at different seasons for the subjects; hence, seasonal variations in serum Vitamin D levels might have affected the comparisons. However, there are conflicting reports regarding the impact of seasonal changes on Vitamin D levels, with some investigators reporting no significant variations in Vitamin D levels with seasonal changes.[29,30]

CONCLUSION

This study showed no significant difference between the serum Vitamin D level of patients with TTH and those of the control group. There was no significant correlation between headache severity and serum Vitamin D level among patients with TTH. Less duration of self-reported exposure to sunlight was found to be a predictor of higher headache disability among TTH patients. There was no predictive relationship between other selected clinical variables (age, sex, body mass index, headache duration, headache frequency, and use of preventive medications) and the severity or intensity of headache in TTH.

ETHICAL CONSIDERATION

Ethical approval was obtained from the Health Research and Ethics Committee of the LUTH before commencement of the study. Written informed consent was obtained from each subject before inclusion in the study. The study was non-interventional and was associated with minimal risk to the participants. The researcher ensured the confidentiality of all participant information and respected the autonomy of participants and the right to decline participation or withdraw participation at any point during the research.

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CONFLICT OF INTERESTS

The authors have no conflict of interest to declare.

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