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Research Submission

Vitamin D Deficiency in Patients With Chronic Tension-Type Headache: A Case-Control Study

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Objective.—To see the interrelation between chronic tension-type headache (CTTH) and serum vitamin D levels.

Background.—Several studies have suggested an association between chronic pain and vitamin D deficiency. Anecdotal evidence suggests that vitamin D deficiency may be associated with tension-type headache and migraine.

Methods.—This case-control study was carried out to examine the association between CTTH and serum 25-hydroxy vitamin (25(OH) D) levels. One hundred consecutive adult (>18 years) patients with CTTH and 100 matched healthy controls were enrolled.

Results.—The serum 25(OH) D levels were significantly lower in CTTH patients than in the controls (14.7 vs 27.4 ng/mL). The prevalence of vitamin D deficiency (serum 25 (OH) D < 20 ng/mL) was greater in patients with CTTH (71% vs 25%). CTTH patients had a significantly high prevalence of musculoskeletal pain (79% vs 57%), muscle weakness (29%vs 10%), muscle tenderness score (7.5 vs 1.9), and bone tenderness score (3.0 vs 0.8) in comparison to controls. CTTH patients with vitamin D deficient group (<20 ng/mL) had a higher prevalence of musculoskeletal pain (58% vs 31%), muscle weakness (38%vs 7%), muscle and bone tenderness score, associated fatigue (44% vs 17%) and more prolonged course (15.5 months vs 11.2 months). A strong positive correlation was noted between serum vitamin D levels and total muscle tenderness score ($R^2 = 0.7365$) and total bone tenderness score ($R^2 = 0.6293$).

Conclusion.—Decreased serum 25(OHD) concentration was associated with CTTH. Intervention studies are required to find out if supplementation of vitamin D is effective in patients with CTTH.

Key words: tension-type headache, chronic-tension-type headache, migraine, generalized pain, osteomalacia, vitamin D

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INTRODUCTION

Several observations have suggested a link between chronic pain and vitamin D deficiency.[1-3] A few recent observations indicate that low serum vitamin D levels may be related to a few headache disorders, especially migraine and tension-type headache (TTH).[4-7]

Muscular factors are very important in the generation of TTH. Pericranial muscular tenderness

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and electromyography changes in these pericranial muscles support this hypothesis.[8] Vitamin D has a significant role in the muscle health.[9] Epidemiological studies suggest a strong association between low serum vitamin D levels and chronic musculoskeletal pain.[1] Therefore, an interrelation between TTH and vitamin D can also be speculated.[4,7] Rickets and osteomalacia are well-known manifestations of vitamin D deficiency. Generalized musculoskeletal pains, bone and muscle tenderness, and muscle weakness/atrophy are common complaints of osteomalacia.[10,11] CTTH patients may also have generalized muscle pain, pericranial and extracephalic tenderness, and neck and other muscle weakness/atrophy.[12-14] Therefore, an overlap between the semiology of TTH and vitamin D deficiency is apparent. In fact, a few studies indicate a possibility of interrelation between vitamin D and TTH. A cross-sectional study has demonstrated significantly low levels of serum vitamin D in nonmigraine headaches (Tension-type headache).[15] Recently, Virtanen et al[16] have demonstrated a strong association ($P < .001$) between low serum vitamin D and frequent headaches (headaches types not described). Prakash et al,[4] in a retrospective observation, noted a high prevalence of vitamin D deficiency in patients with CTTH. A few case reports have also demonstrated the beneficial effects of vitamin D supplementation (with calcium) in patients with CTTH.[7,17]

The prevalence of vitamin D deficiency is very high in the generation population. Therefore, interpretation of its effects should be careful. A case-control study can represent the best option. This case-control study was undertaken to find out the interrelation between serum vitamin D levels and CTTH.

MATERIALS AND METHODS

The study was done in a neurology outpatient clinic of a large tertiary hospital between February 2015 and October 2016. The Institutional Ethic Committee approved the study protocol (SVRC/ON/MEDZ/FP/15009). Subjects were enrolled only after getting a written informed consent. This is a one time study and no data have been published previously. We have no plan to perform any further analyses of these data in the future.

Sample Size Calculation.—The study was designed to detect a mean difference of serum vitamin D levels of 5 ng/mL between matched participants. The standard deviation was assumed to be 10 ng/mL based on the observations in the general population of the geographic region of the study population.[18] The prevalence of CTTH is about 2% in the general population. With 95% confidence level ($\alpha = 0.05$) and 80% statistical power ($\beta = 0.20$), the calculated sample size was 72 matched pairs. However, we planned to recruit a minimum of 100 matched pairs to minimize the effects of heterogeneous population.

Study Population.—One hundred consecutive adults (>18 years) with CTTH were included. All patients fulfilled the international classification of headache disorders (ICHD-3β) criteria of CTTH.[19] The patients should not have more than one of photophobia, phonophobia, or mild nausea and neither moderate nor severe nausea nor vomiting as defined by ICHD-3β criteria for CTTH.[19] Exclusion criteria for the cases were as follows: (i) age <18 years; (ii) CTTH-like headache with acute onset (to exclude NDPH); (iii) patients with a history suggestive of migraine headache in the past (to minimize the possibility of chronic migraine); (iv) had taken vitamin D supplements in the previous 4 weeks; (iv) patients having a history of any acute or chronic disorders (including diabetes mellitus, hypertension, thyroid disorders, epilepsy, Parkinson's disease, Alzheimer's disease, stroke, brain tumors, palsy of any limb, etc) to avoid the possible confounders.

One hundred healthy adults were enrolled as controls. The person who has no headache or headache less than one attack per month in the last 3 months was considered as a control. Control subjects were selected from the subjects who have come to the hospital along with other patients attending for a complaint other than headaches (ie, controls were nonconsanguineous relatives of patients attending neurological outpatient clinic). The control was matched for the age (±4 years), gender, weight (±5 kg), season enrolled (within 2

week), education level (<10 years vs >10 years), and socioeconomic status. The exclusion criteria for controls were the same as for the cases. The controls had not suffered from any acute or chronic illness and had a normal neurological examination. The questionnaires for both patients and controls were completed by the corresponding author (a neurologist and headache expert).

Clinical Assessment.—Face-to-face interviews were conducted using a structured questionnaire and proforma. Patients underwent a detailed physical and neurological examination. All patients were subjected to MRI of the brain to rule out intracranial pathologies. The data were recorded by the corresponding author

The questionnaires included the following details: demographic characteristics (age, gender, weight, height, BMI, education level, etc), age at onset (duration of illness), headache characteristics (frequency, location, duration of attacks, severity, character, precipitating factors, etc), and associated features. The patient was asked about the presence of pain (other than headache) at any other site of the body. The sites of the musculoskeletal pain were noted according to the American College of Rheumatology (ACR) criteria for chronic widespread pain (CWP).[20] The sites include neck, back (upper and lower), upper limbs, and lower limbs. The pain at extracranial sites was assessed by asking whether the patient had pain at these sites or not (yes/no format). The severity of the musculoskeletal pain was not graded.

Smokers were defined as people who had smoked ≥1 cigarettes per day during the last 1 year. The quantification of alcohol intake is hard to ascertain in our country as this information is rarely revealed. Therefore, any individual that stated they consumed alcohol was considered a drinker. Sunlight exposure was not assessed because of the various constraints.

Clinical Examinations.—Manual palpation for muscle tenderness was done for pericranial and extracephalic muscles. Pericranial muscles include: (i) frontalis muscle, just above the supraorbital notch, (ii) anterior temporalis muscle, and (iii) suboccipital muscles at the suboccipital fossa. Extracephalic muscles were: (i) elbow, 2 cm distal to the lateral epicondyle, (ii) medial fat pad of the knee, proximal to the joint line, (iii) Achilles tendon, 1 cm above the calcaneum. Symmetrical muscles were palpated. Tenderness was graded according to a 4-point scale (0-3). The grade was defined as follows: 0 = denial of tenderness; 1 = no visible facial reaction, but a verbal report of mild pain; 2 = verbal report of painful tenderness with the facial reaction of the discomfort; and 3 = report of severe pain and marked grimacing. A Total Tenderness Score (TTS) was calculated by the simple addition of the scores for the each patient. As most studies have not revealed any side-to-side variability in the tenderness score, score of only one side was considered for the calculation.

A physical examination for bone tenderness was also performed. We applied firm pressure with the thumb or forefinger on the anterior tibia, and radius or ulna (as suggested by various authors).[21] Bone tenderness was graded as muscle tenderness (0-3).[4] TTS for the bones was calculated separately.

We examined the muscle power at every joint in details to find out any subtle weakness. It was graded according to the Medical Research Council scale.

Laboratory Investigations.—Routine biochemical investigations, including a complete hemogram, ESR, blood sugar, liver, and kidney function tests were done in all patients.

Vitamin D Estimation.—Nonfasting venous blood samples were collected for serum 25(OH) D estimation. Serum was prepared and it was stored at −20 degrees C until further analysis. Serum 25-(OH) vitamin D was estimated using the enzyme immunoassay kit (vitamin D the enzyme immunoassay kit; Bio-Detect, CA, USA). The procedure was performed according to the instructions provided by the manufacturer. Normal levels of vitamin D were defined as serum levels >30 ng/mL. Vitamin D deficiency and insufficiency were defined as serum concentrations of 25(OH) D < 20 ng/mL, and 20 to <29.9 ng/mL, respectively.[21]

BIOSTATISTICS

Descriptive statistics for both the cases and controls were tabulated. Data are presented as

Table 1.—Demographic Characteristics of Patients With Chronic Tension-Type Headaches and Healthy Controls

Parameters	Patients (n-100) (n=%)	Controls (n-100) (n=%)	*P* Value
Age (mean ± SD)	35.63 ± 12.2	36.76 ± 12.3	.515
Sex, Female (n, %)	63 (63%)	61 (61%)	.884
BMI	23.9 ± 2.2	23.7 ± 2.3	.530
Smoking	13	17	.553
Drinking alcohol	12	9	.645
Residence			
Rural	62	65	.769
Urban	38	35	
Education level			
<10 yrs education	35	45	.193
≥10 yrs education	65	55	
Season enrolled			
Summer-Fall	54	51	.777
Winter-Spring	46	49	
Serum vitamin D			
mean ±SD (ng/mL)	14.72 ± 8.5	27.35 ± 10.2	<.001*
<20.0 ng/mL	71	25	<.001*
20-29.9 ng/mL	23	38	.031*
>30 ng/mL	6	37	<.001*

*$P < .05$.

percentages or as arithmetic mean with SD. Student's *t*-test was used to compare the continuous data. The chi-square test with Yates's correction or Fisher exact was used for the categorical data. In addition, the odds ratio (OR) with 95% confidence interval (CI), when deemed necessary, was calculated. The correlation between serum 25(OH) D concentration and various clinical features were assessed by Pearson's correlation coefficient or simple logistic regression (or scatter plot).

The association of serum 25-OHD levels and CTTH was determined by calculating odds ratio (OR) and corresponding 95%CI using multiple logistic regression. It was carried out using different models. The first model was a crude model with no adjustment for confounders. The final model was created by adding potential confounders. Potential confounders were included and retained in the model if they changed the unadjusted OR by more than 10%. The potential confounders include age, sex, BMI, smoking, alcohol intake, season enrolled, residence (rural or urban), and education.

All *P* values were two-tailed, and a *P* value <.05 was considered as statistically significant. Bonferroni adjustments were applied when necessary with the significance level set to $P < .017$ (0.05/3 dependent variables). All analyses were processed by SPSS 22.0.

RESULTS

A total of 157 patients with a diagnosis of CTTH were evaluated during the study period. Fifty-seven patients were excluded for the following reasons: (i) age less than 18 years: 8 patients, (ii) a diagnostic overlap with either chronic migraine or NDPH: 19 patients, (iii) a history of associated diseases: 15 patients (diabetes mellitus-4 patients; hypertension-3; hypothyroidism-2; stroke-2; Parkinson's disease-1; ischemic heart disaease-1; chronic obstructive pulmonary disease-1; and fibromyalgia-1 patient, (iv) not subjected to neuroimaging: 4 patients, (v) receiving vitamin D supplementation: 8 patients, (vi) refused to participate in the study: 3 patients. We recruited 100 patients with CTTH

Table 2.—Risk of Chronic Tension-Type Headache (CTTH) According to Levels of 25-Hydroxyvitamin D (25[OH] D)

	Logistic Regression.					
	Unadjusted			Adjusted[a]		
Patients −100 Controls −100	OR	CI	*P* Value	OR	CI	*P* Value
Serum vitamin D level						
>30 ng/mL	1	Reference	-	1	Reference	-
30-20 ng/mL	3.73	1.36-10.20	.01*	3.91	1.01-11.02	.01*
<20 ng/mL	17.51	6.60-46.46	<.001*	17.71	7.11-47.57	<.001*

CI = confidence interval; OR = odds ratio.
a = Adjusted for age, gender, BMI, alcohol intake, season enrolled, education status, residence (rural or urban).

over 21 months. In parallel, 100 matched healthy controls were recruited.

Demographic Characteristics.—The demographic data and serum vitamin D levels of all patients and controls are summarized in Table 1. There were no significant differences in age, sex, age, BMI, smoking status, alcohol drinking, residence, educational status, and season enrolled between patients and healthy controls. The subjects with CTTH had a mean age of 35.6 ± 12.2 years and a female/male ratio of 63/37. The controls had a mean age of 36.8 ± 12.3 years and a female/male ratio of 61/39.

Serum 25(OH) Vitamin D Levels.—The mean serum level of vitamin D was significantly lower in CTTH group than in the controls. The mean ± SD concentration of vitamin D was 14.7 ± 8.5 ng/mL in CTTH patients and 27.4 ± 10.2 ng/mL in controls ($P < .001$). The proportion of serum 25-OHD deficiency (<20 ng/mL) was significantly higher in cases than in controls (71% vs 25% OR = 7.3 [95% CI, 3.9-13.7], $P =< .001$). The prevalence of normal vitamin D levels (>30 ng/mL) was significantly lower in cases than controls (6% vs 37%, $P < .001$).

Table 2 shows univariate and multiple logistic regressions between serum vitamin D levels and the CTTH. Vitamin D insufficiency was associated with CTTH in both unadjusted (OR = 17.5 [95% confidence interval: 6.6-46.4 $P =< .001$] and adjusted logistic regression (OR = 17.71 [95% confidence interval: 7.1-47.6, $P =< .001$].

Clinical Features.—Headache characteristics of cases are summarized in Table 3. Headache attack days were >15 days/month for all patients (as a part of the inclusion criteria of CTTH). However,

Table 3.—Headache Characteristics of Cases (Chronic Tension-Type Headache)

Headache Characteristics	Number (n) (n = %)
Duration of illness (months)	14.3 ± 7.8
Bilateral	100
Intensity	
Mild-moderate intensity	100
Severe intensity (superimposed)	26
Frequency	
> 15 days/month (as a part of CTTH criteria)	100
Near daily headache (30 days/month)	34
Character	
Nonthrobbing	100
Throbbing	24
Duration of headache attacks	Highly variable
Other associated features	
Nausea	12
Vomiting	0
Phonophobia	29
Photophobia	4

Table 4.—Clinical Characteristics of Cases (CTTH Patients) and Controls

Clinical Features		Cases (n-100) (n = %)	Controls (n-100) (n = %)	*P* Value
Fatigue n = %		36	18	.006*
Depression (self-reported) n = %		28	18	.130
Anxiety (self-reported) n = %		17	11	.308
Musculoskeletal pain n = %				
Cervical		48	29	.009*
Upper back/Thoracic spine		39	20	.005*
Lower back/Lumbosacral spine		50	22	<.001*
Shoulder		21	11	.081
Buttock		14	7	.165
Upper limb		25	11	.015*
Lower limb		28	12	.007*
Chronic widespread pain		19	2	<.001*
At least one segment		79	57	.001*
Muscle tenderness score (n-number of patients, mean ± SD) (n = %)				
Temporalis	n	89	42	<.001*
	score	1.9 ± 0.9	0.59 ± 0.8	<.001*
Frontalis	n	65	21	<.001*
	score	1.01 ± 0.9	0.21 ± 0.4	<.001*
Suboccipital	n	78	36	<.001*
	score	1.41 ± 0.9	0.36 ± 0.5	<.001*
Elbow	n	71	30	.0001*
	score	1.19 ± 0.9	0.30 ± 0.5	.0001*
Thigh	n	64	21	.0001*
	score	0.96 ± 0.8	0.21 ± 0.4	.0001*
Achilles	n	64	23	.0001*
	score	1.01 ± 0.8	0.23 ± 0.3	.0001*
Total score	score	7.47 ± 4.5	1.85 ± 2.2	.0001*
Bone tenderness score (n-number of patients, mean score ± SD)				
Radius-ulna	n	88	41	.0001*
	score	1.65 ± 0.9	0.45 ± 0.6	.0001*
Anterior tibia	n	73	30	.0001*
	score	1.26 ± 0.9	0.32 ± 0.5	.0001*
Total score		2.98 ± 1.7	0.77 ± 0.9	.0001*
Muscle weakness n = %				
Lower limb weakness		29	10	.0011*
Upper limb weakness		17	7	.0484*
Neck muscle		12	3	.0287*

*$P < .05$.

one-third of patients (34%) reported headache on the daily basis (30 days/month, ie, no headache free day). Other clinical details of both cases and controls are summarized in Table 4. It compares fatigue, depression (self-reported), anxiety (self-reported), pain at other sites (ie, other than headache), muscular tenderness (number of patients and tenderness score), bone tenderness, and muscular weakness (lower limb and upper limb).

Fatigue was significantly associated with CTTH group (36% vs 18%, $P = .006$). The musculoskeletal pain was common at all sites (neck, upper back, lower back, shoulder, upper limbs, buttock, and lower limbs) in patients with CTTH. However, the differences were statistically significant for pain in the neck ($P = .008$), upper back ($P = .005$), lower back ($P = < .001$), upper limb ($P = .015$), and lower limb ($P = .007$). Nineteen patients (19%) with

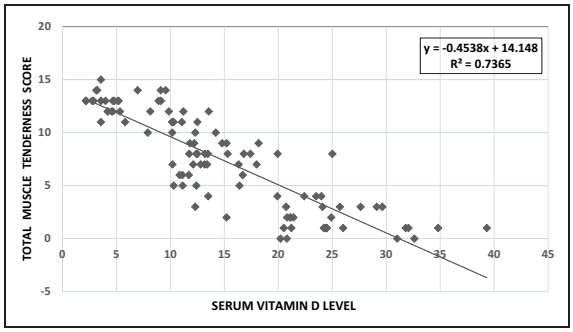

Fig. 1.—Correlation between serum 25(OH) D and total muscular tenderness.

CTTH and two controls (2%) reported pain in the multiple regions that satisfied the ACR criteria for CWP ($P = .001$).

Tenderness.—Muscular tenderness for both cephalic and extracephalic regions was significantly associated with CTTH. This association was significant in relation to both number of patients involved and total muscular tenderness score ($P = < .001$, at all muscles). A similar observation was noted for even bone tenderness ($P = < 0.001$).

A strong positive correlation was noted between serum vitamin D level and to both total muscle tenderness score ($R^2 = 0.736$) and total bone tenderness score ($R^2 = 0.629$) (Figs. 1 and 2).

Weakness.—The prevalence of muscle weakness was higher in patients with CTTH, and it was statistically significant (lower limb-29% vs 10%, $P = .001$; upper limb-17% vs 7%, $P = .048$; neck muscle- 12% vs 3%, $P = .029$).

Subgroup Analyses.—Post hoc comparisons among different clinical groups were made.

CTTH patients with serum vitamin D < 20 ng/mL (71%) vs with > 20 ng/mL (29%): No statistically significant differences in age, gender, residence, season enrolled, smoking habit and drinking habit (Table 5) were noted. The headache was statistically more chronic in patients with <20 ng/mL (15.5 ± 8.5 months vs 11.2 ± 4.9, $P = .013$). Daily or near daily headache was also statistically more prevalent in patients with < 20 ng/mL serum vitamin D (41% vs. 17%, $P = .035$). Fatigue was also more frequent in vitamin D deficient patients and it was statistically significant (44% vs 17%, $P = .012$). Both muscle tenderness score and bone tenderness score were significantly higher at all regions in the vitamin D deficient person.

"Headache only" (21%) vs "headache and musculoskeletal pain" (79%): 79% of patients had musculoskeletal pain at least in one region (Table 6). Patients with both 'headache and musculoskeletal pain' had significantly lower mean 25(OH) D levels (12.8 ± 7.3 vs 21.7 ± 9.0, $P = < .001$). These patients had a significantly higher prevalence of fatigue (43% vs 10%, $P = .0001$, total muscle tenderness score (8.5 ± 4.2 vs 3.6 ± 3.1, $P = < .001$, total bone tenderness score (3.3 ± 1.5 vs 1.5 ± 1.5, $P = < .001$, and lower limb weakness (34% vs 10%, $P = .031$). Upper limb weakness and neck muscle weakness were also higher in patients CTTH and musculoskeletal pain together. However, it did not achieve significant P value.

"Daily or near daily headache" (34%) vs "less frequent headache" (66%): Patients with near daily headache had significantly lower mean 25(OH) D levels (9.9 ± 7.3 vs 17.1 ± 8.0, $P = < .001$). There were no statistically significant differences in age, gender, residence, and season enrolled. These patients with near daily headache had significantly higher score of total muscle tenderness score (9.9 ± 3.8 vs 6.2 ± 4.3, $P = < .001$, and total bone tenderness score (3.8 ± 1.5 vs 1.5 ± 1.6, $P = < .001$). Lower limb weakness was also significantly high in near daily headache group (47% vs 20%, $P = .022$). Fatigue upper limb weakness and neck muscle weakness were also higher in patients with daily headaches. However, it did not achieve significant P value (not shown in table).

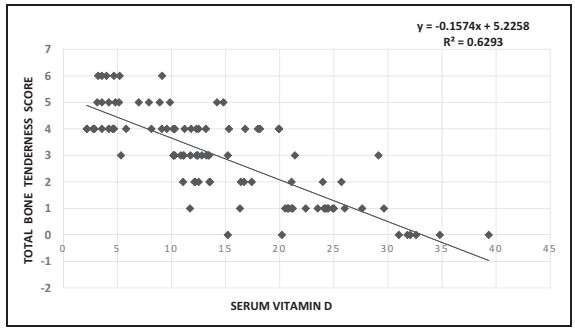

Fig. 2.—Correlation between serum 25(OH) D and total bone tenderness score.

Table 5.—A Comparative Data of Cases (CTTH), According to Categories of 25 Vitamin D Levels

Parameters	Serum Vitamin D < 20 ng/mL (n-71)	Serum vitamin D > 20 ng/mL (n-29)	*P* value
Age (yrs) (mean ± SD)	34.46 ± 12.1	38.48 ± 12.1	.134
Sex, Female n (%)	45 (63%)	18 (62%)	1
BMI (mean ± SD)	23.8 ± 2.3	24.3 ± 2.0	.415
Residence – Rural n (%)	40 (56%)	22 (76%)	.074
Education (<10 yr education) n (%)	26 (37%)	9 (31%)	.650
Season enrolled (Summer-Fall) n (%)	34 (48%)	20 (69%)	.076
Headache characteristics			
Duration of illness (months) (mean ± SD)	15.5 ± 8.5	11.24 ± 4.9	.013*
Severe exacerbations n (%)	20 (28%)	6 (21%)	.616
Daily headache n (%)	29 (41%)	5 (17%)	.035*
Other clinical features			
Fatigue n (%)	31 (44%)	5 (17%)	.013*
Depression (self-reported) n (%)	19 (27%)	9 (31%)	.806
Anxiety (self-reported) n (%)	11 (15%)	6 (21%)	.563
Musculoskeletal pain			
Cervical n (%)	39(55%)	9 (31%)	.046*
Lower back n (%)	41(58%)	9 (31%)	.027*
Muscle tenderness score (mean ± SD)			
Temporalis	2.3 ± 0.6	0.68 ± 0.5	<.001*
Frontalis	1.33 ± 0.8	0.21 ± 0.4	<.001*
Suboccipital	1.85 ± 0.5	0.31 ± 0.5	<.001*
Elbow	1.56 ± 0.7	0.27 ± 0.4	<.001*
Thigh	1.26 ± 0.8	0.21 ± 0.4	<.001*
Achilles	1.28 ± 0.8	0.31 ± 0.5	<.001**
Total score	9.70 ± 3.12	2.00 ± 1.7	<.001*
Bone tenderness score (mean ± SD)			
Radius-ulna	2.04 ± 0.6	1.65 ± 0.9	<.001*
Anterior tibia	1.64 ± 0.8	1.26 ± 0.9	<.001*
Total score	3.69 ± 1.7	2.91 ± 1.6	<.001*
Muscle weakness n (%)			
Lower limb weakness	27 (38%)	2 (7%)	.001*
Upper limb weakness	16 (23%)	1 (3%)	.020*
Neck muscle weakness	10 (14%)	2 (7%)	.500

*$P < .05$.

DISCUSSION

The main finding of the present case-control study is that patients with CTTH had significantly lower serum 25(OH) D levels. In addition, CTTH patients had symptoms pertinent to vitamin D deficiency (fatigue, musculoskeletal pain, muscle and bone tenderness, and proximal limb weakness).

Kjærgaard et al,[15] in a cross-sectional study on 11,614 persons, have demonstrated a significantly low level of serum 25(OH) D in nonmigraine headache (probably TTH). In another cross-sectional study, Knusten et al[22] observed the lower levels of serum 25(OH) D in patients with musculoskeletal pain, fatigue, and headache (headache was not classified). The mean serum vitamin D level was much lower in patients with headaches compared to patients with other symptoms.

A few case-control studies have also been done in headache patients. Sonmez et al[23] noted significantly lower levels of vitamin D in both migraine and TTH in a case-control study in children (published in abstract). Celikbilek et al[5] noted significantly lower level serum 25(OH) D in patients with migraine. However, in another case-control study, the authors did not find any correlation between serum vitamin D level and migraine.[24] To the best of

Table 6.—A Comparison Between CTTH Patients Having "Headache Only" and Having Both "Headache and Musculoskeletal Pain"

Parameters	CTTH with Musculoskeletal Pain (n-79)	Isolated CTTH Only (n-21)	*P* Value
Age (years) (mean ± SD)	35.9 ± 12.6	34.3 ± 10.9	.643
Duration of illness (months) (mean ± SD)	14.9 ± 8.2	11.81 ± 5.8	.107
Daily headache n (%)	30 (38%)	4 (19%)	.096
Fatigue n (%)	34 (43%)	2 (10%)	<.001*
Total muscle tenderness score (mean ± SD)	8.5 ± 4.2	3.6 ± 3.1	<.001*
Total bone tenderness score (mean ± SD)	3.3 ± 1.5	1.5 ± 1.5	<.001*
Lower limb weakness n (%)	27 (34%)	2 (10%)	.030*
Upper limb weakness n (%)	15 (19%)	2 (10%)	.513
Neck muscle weakness n (%)	11 (14%)	1 (5%)	.451
Serum vitamin D level (ng/mL) (mean ± SD)	12.8 ± 7.3	21.7 ± 9.0	<.001*

*$P < .05$.

our literature search, there is no case-control study on the relation of vitamin D and CTTH in the adult.

Vitamin D and Headache: Any Clinical Overlap?—Several studies have demonstrated a positive link vitamin D deficiency and diffuse musculoskeletal pain.[1-3] Nonspecific musculoskeletal pain usually precedes the vitamin D related bone pain (osteomalacic bone pain).[3] An evaluation of serum vitamin D level has been recommended for the generalized musculoskeletal pain.[2,3]

ICHD-3β classifies TTH: (i) with pericranial tenderness and (ii) without pericranial tenderness (17).[17] However, tenderness may be noted even in extracephalic muscles.[25] Hagen et al[26] have shown a bidirectional relationship between chronic musculoskeletal symptoms and chronic headaches. In another study, they reported the prevalence of chronic headache 4 times greater in patients with chronic musculoskeletal symptoms compared to participants without such symptoms.[27] Our 79% CTTH patients had musculoskeletal pain at least at one site. CWP was noted in 19% cases. Extracephalic muscular tenderness is well reported with CTTH. Muscle tenderness was statistically significant in both pericranial and extracranial muscles in our CTTH patients. We also noted statistically significant bone tenderness. The serum vitamin D levels were significantly lower in patients having both musculoskeletal pain and headache together than patients with headache only (Table 6). Therefore, based on these similarities, we can speculate on that chronic musculoskeletal pain with CTTH may be related to low vitamin D levels in a subset of patients.

Headache and Weakness.—Weakness in vitamin D deficiency is usually explained by osteomalacic myopathy.[12,28] The incidence of myopathy in osteomalacia varies from 73% to 97%. Weakness may be the initial symptom in 30% cases of osteomalacia.[28] The severity varies from a mild weakness, noticeable only on careful neurological examination, to severe disability leading to complete paralysis. Recent advances suggest that vitamin D deficiency may cause muscle weakness even without having bone pathology (osteomalacia).[2,29]

We noted statistically significant weakness in all these three groups of muscles (lower limb *P* value = .001; upper limb *P* value = .048, neck muscle *P* value = .028). There are a few studies in the literature where muscle power was tested in the neck and shoulder muscle in patients TTH. Madsen et al[13] compared the muscle strength in the neck and shoulder muscles in TTH to healthy controls. They noted statistically significant decrease in muscle strength in the neck extension and shoulder abduction. Therefore, it can again be speculated that weakness in the neck and shoulder muscles in patients with CTTH could be because of associated

vitamin D deficiency in a subset of patients with CTTH (especially CTTH patients with musculoskeletal pain).

Headache and Muscle Atrophy.—Vitamin D deficiency is known to produce type II muscle atrophy.[11,28] The atrophy related to vitamin D deficiency can be picked up at an early stage by various imaging methods.[30] Fernández-de-las-Peñas et al[14] studied the differences in the relative cross-sectional area (rRCSA) of cervical extensor muscles by magnetic resonance imaging (MRI), between patients with CTTH and healthy controls. The (rRCSA) of the various extensor muscles was reduced in patients with CTTH. The reduction in (rRCSA) was negatively associated with the intensity, duration, and frequency of headache. It again raises a possibility of associated vitamin D deficiency in such patients.

PATHOPHYSIOLOGY

Pathophysiology in CTTH.—Both peripheral (myofascial nociception) and central mechanisms have been suggested for the generation of TTH. Peripheral mechanisms have a major role in episodic TTH. Central mechanisms (including central sensitization) predominate in CTTH. The chronic musculoskeletal pain in the headache patients is typically explained by the development of central sensitization.[31] However, the cause-effect relation for neck/shoulder muscle weakness and atrophy of neck muscles associated with CTTH is still to be determined.

Pathophysiology for Vitamin D Deficiency Related Pain.—As discussed, both skeletal (bone) and muscular factors are involved in the generation of musculoskeletal pain. Usually, muscle related pain precedes bone related pain.[3]

Skeletal Factors.—It is suggested that, in osteomalacia, bone develops swollen deposition of osteoid on the periosteal surface of the skeleton. This swollen deposition exerts an outward pressure on the periosteal covering that is innervated by sensory pain fibres (nociceptors). This is largely responsible for the bone and muscle pain in osteomalacia.[3,21]

Muscular Factors.—Tague et al have demonstrated vitamin D receptors in 'pain-sensing' nerves, which increase in vitamin D deficient states (sensory hyperinnervation).[32] They have also demonstrated muscle hypersensitivity (without cutaneous hypersensitivity) in rats receiving vitamin D-deficient diets.[33] Sensory hyperinnervation and muscle hypersensitivity may be one of the mechanisms for the generation of musculoskeletal pain in patients with vitamin D deficiency. It usually precedes the development of skeletal pathology (osteomalacia) in vitamin D deficiency

Atrophy of a certain group of muscles (type II muscle fibers) may produce mechanical stress on the remaining muscle. The mechanically overloaded muscle may predispose to the formation of myofascial trigger points (TrPs) (a feature well known in TTH).[34] Therefore, the osteomalacic myopathy may increase the TrPs formation.

There is another suggestion that vitamin D deficiency may increase the central sensitization for the pain.[35]

Pathophysiological Interrelation Between CTTH and Vitamin D Deficiency.—Pericranial muscles and bones of the skull are not different from the muscles and bones of other part of the body. Therefore, Prakash et al[4] speculate that vitamin D deficiency may also affect the skull and pericranial musculature in the same fashion. The literature is silent over the involvement of the skull in patients with vitamin D deficiency in adult (osteomalacia). However, bone abnormality in the skull is reported in rickets (vitamin D deficiency in children). Craniotabes with the abnormal consistency of the skull is an important feature of rickets.[11] Craniotabes may be the first symptom of sub clinical vitamin D deficiency in children.[36]

Therefore, it can be speculated that involvement of the skull and pericranial muscle may present as head pain and pericranial tenderness in a vitamin D-deficient person. Neck and shoulder muscle weakness and atrophy of the neck muscles with CTTH could also be explained by vitamin D deficiency in a subset of patients.

The cooccurrence of headache and generalized pain is either explained by central sensitization or by two different conditions. We suggest that the presence of both CTTH and generalized musculoskeletal pain together in a patient could be because of a common etiology/pathophysiology. Vitamin D deficiency could be an important cause for such combination.

However, a few other speculations can also be made here. Chronic headache patients have limited physical activities (including limited outdoor activities). Any patient with reduced outdoor activities are prone to develop vitamin D deficiency. Therefore, it could be presumed that vitamin D deficiency in CTTH is just a secondary phenomenon and vitamin D deficiency is not causally related to the development of headaches.

Moreover, limited physical activity in headache patients may lead to the deconditioning of muscle functions. This may be the reason for the reduced muscle strength, and there may not be any causal association between reduced vitamin D level and muscle weakness in these patients.

LIMITATION

This observation was done on convenience samples from an adult tertiary neurology clinic. Therefore, these observations cannot be generalized, as it may not truly represent CTTH patients due to referral and other biases. Being a clinic-based observation, it may also be representative of more severe cases of CTTH. Moreover, it is a single-center study; replication from other centers is required. Serum vitamin D levels vary with a large number of factors, including latitude. Therefore, multicentric studies are required to see whether these results apply across different settings.

Although common causes of secondary generalized pain were ruled out by a good history taking, physical examinations, and appropriate investigations; a possibility of other secondary causes of musculoskeletal pain cannot be ruled out completely. A few patients have either isolated nausea or isolated photophobia or phonophobia. Therefore, a possibility of migraine or coexistent migraine cannot be ruled out completely.

Although we have included a few confounders in the data analysis, a possibility of other unrecognized confounders cannot be ruled out. A few confounders (such as alcohol intake, sun exposure duration, fatigue, etc) could not be quantified because of the various reasons. Moreover, we did not include any depression scale in this study.

In addition, ELISA assay has some limitation. Therefore, this observation should be confirmed by mass spectrometry, which is superior for measuring 25(OH) D levels.

As it is difficult to find out any causal association with a cross-sectional study, intervention studies are required to find out any causal association.

CONCLUSION

Vitamin D deficiency closely mimics CTTH. However, as vitamin D deficiency is common in the general population, both conditions may be just a comorbid state in the same patient, producing an overlapped clinical features. However, identifying even this comorbid condition may be important for therapeutic purposes.

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