

Vitamin D, Chronic Migraine and Extracranial Pain: Is there a Link? Data from an Observational Study.

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Abstract

Background: Several studies focused on the possible role of vitamin D (vitD) in pain chronicization.. The aim of this study was to assess the potential implications of VitD deficit on headache characteristics and extracranial pain extension.

Methods: Eighty consecutive patients with primary headache underwent neurological examination, laboratory exams including serum calcifediol 25(OH)D and headache features assessment along with three questionnaires investigating depression, anxiety and allodynia.

Results: The 82.6% of the population had migraine (48% episodic and 52% chronic form). The 45% of patients had extracranial pain and 47% suffered from allodynia. In the 45% of patients had a VitD deficit since the serum 25(OH)D levels fell below the cut-off level of 20 ng/ml. The occurrence of VitD deficit was significantly higher ($p=0.009$) in patients suffering from chronic migraine (CM)- medication overuse migraine (MOH) (64.7%) than in episodic migraine (EM) or tension type headache (TTH). The occurrence of subjects with extracranial pain and allodynia was higher, as expected, in the CM-MOH than in the EM and in the TTH groups but was not related to the co-occurrence of vit-D deficiency (Fischer's exact test $p=0.11$ and $p=0.32$ respectively).

Conclusions: Our findings show that 25(OH)D deficit is related to chronic pain suggesting that vitD probably has anti-inflammatory and tolerogenic properties, rather than a direct antinociceptive effect, and reinforce the idea of a neuroinflammatory mechanisms underpinning migraine chronicization.

Background

Migraine and Tension Type Headache (TTH) are common disorders, affecting up to 22% and 78% of the population, respectively (1, 2). Although migraine and TTH are generally episodic and regress taking symptomatic treatments, they may become chronic and necessitate prophylaxis. According to epidemiological studies, each year the 2.5% of episodic migraineurs (EM) progress to chronic migraine (CM), which is characterized by the occurrence of at least 15 migraine attacks per month (3–5). CM may favor the development of a wide spectrum of co-morbidities, such as psychiatric and sleep disorders, metabolic alterations, along with other forms of pain such as TTH, medication overuse headache (MOH), diffuse and persistent pain (matching the American College of Rheumatology criteria for fibromyalgia-FMS), chronic fatigue pain, myofascial and musculoskeletal pain(1). Accordingly, more than 70% of patients with FMS complain of headache (4–6). The mechanisms leading from EM to CM are not fully understood. Cortical excitability appears to be abnormal in CM patients, compared to EM patients, but this could be a consequence of the disease itself (3). The role and the contribution of inflammation and central sensitization have been considered (7).

Recently, several studies focused on the possible role of micronutrients and especially of vitamin D (vitD) in chronic pain development.

The role of vitamin D in the pathogenesis of pain and headache

Circulating VitD mostly derives from the activation of its endogen precursor (7-dehydrocholesterol) in the epidermis by ultraviolet B radiation, followed by two consecutive hydroxylations (8, 9). In the last decades, a tissue-local production of active VitD was demonstrated (9). Besides the undoubted involvement of VitD in musculoskeletal health, several preclinical studies supported a larger spectrum of activities (8, 10, 11). VitD acts as a developmental neuroactive steroid, influencing various functions of the nervous system and neurotransmitters levels (12, 13). VitD receptors, along with the enzymes involved in VitD synthesis and degradation (25-hydroxylase, 1 α -hydroxylase, 24-CYP24A1), are expressed by neurons, astrocytes and oligodendrocytes distributed in brain regions (14–19), which are therefore able to independently synthesize active VitD and to regulate its local concentrations (12, 16). In the striatum and substantia nigra, VitD seems to be involved in dopamine neurons survival as well as in tonic and phasic dopamine release (20–22). Groves and coworkers(23) demonstrated that VitD deficient diet reduced the expression of enzymes involved in gamma-aminobutyric acid (GABA) synthesis, as confirmed by further experiments(17). Notably, Vit D regulates serotonin neurotransmission through the genomic regulation of tryptophan hydroxylase 2 (TPH2) (2, 17). As central nervous system (CNS) cells, most of immune cells express the vitD receptors and the enzymes involved in VitD synthesis and degradation (10). *In vitro* and animal experimental studies could demonstrate that VitD promoted anti-inflammatory and tolerogenic behaviors in both innate and adaptive immune cells, at expense of proinflammatory subsets (8, 13). Several studies agreed on the existence of a relationship between VitD levels and pain, especially FMS, musculoskeletal pain and headache (24–27). To our knowledge, just a few reports explored the role of VitD on pain chronicization.

Materials And Methods

Our observational study aimed at investigating the potential implications of VitD status on headache characteristics and extracranial pain extension.

Subjects

On the basis of literature data, starting from January 2017 to December 2018, all the patients attending our Centre with a diagnosis of primary headache, were screened with routine laboratory exams and VitD dosage. Retrospectively we considered the data from eighty patients who were older than 18 years and that were not pregnant, not suffering from active neoplasia, malabsorption, severe kidney and cardiovascular disorders, not taking supplementation with VitD and/or calcium or multivitamin drugs or a treatment for osteoporosis. The patients were divided into 6 diagnostic subgroups depending on the ICHD-3 criteria(5): EM with and without aura, CM, MOH, TTH and chronic TTH. For each patient we acknowledged: age, sex, height, weight, body mass index (computed as index and recoded as underweight if < 18.49 Kg/m², normal if between 18.5 and 24.99 Kg/m², overweight if between 25 and

29.99 Kg/m² and obese if ≥ 30 Kg/m²), episodes frequency and use of symptomatic drugs that were recorded on specific diaries, the occurrence of extracranial pain (neck, upper and lower back, upper and lower limbs) and allodynia, defined as an Allodynia Symptoms Check (ASC-12) score > 2 with the validated “12-item Allodynia Symptom Check list” (28). We also acknowledged: job, physical activity, dairy intolerance, co-morbidities and family history of headache. We administered two questionnaires to each patient: the “Hospital Anxiety and Depression Scale-Anxiety (HADS-A)”, which is a well-validated tool to test the presence of depression and anxiety in somatic patients (29–32), and the “Fatigue Severity Scale (FSS)”, that investigates fatigue. The HADS-A scale consists of 7 items, each with 4 answer options (scored between 0 and 3 points). The final score defines the absence of anxiety (< 7 points), a mild form (8–10 points), a moderate form of anxiety (11–14 points) or a serious disturbance (15–21 points). The FSS questionnaire evaluates the impact of fatigue through 9 items, each scored from 1 to 7 points, building a final score between 9 and 63 points (33, 34). The study was conducted in accordance with the “Declaration of Helsinki” and “Good Clinical Practice guidelines”. For this kind of study in which the data are collectable from the clinical records of the patients, we are not required to have a specific permission from the local ethical committee-

Blood samples

Fasting venous blood samples were taken in the morning. Serum calcifediol (25(OH)D) concentration is widely considered the most reliable indicator of VitD reserve, reflecting both dietary intake and exposure to UV radiation. Serum (25(OH)D) levels were assessed by chemiluminescence assay (sensitivity 1.5 ng/ml, precision interval 7–11%). The definition of VitD status is still on debate. In this study, according to recent position statement, VitD status was categorized as insufficient for 25(OH)D values < 20 ng/ml (35, 36). Intact parathyroid hormone (PTH) was measured by a 2-step immunoradiometric assay, sensitivity 1 pg/ml, normal range 15–88 pg/ml. Normal values for chemistry and hematology determinations were as follows: calcium (8–10 mg/dL), folates (8.1–45 nmol/L), vitamin B12 (133–675 pmol/L); homocysteine (< 12 μ mol/L), iron (33–193 μ g/dL), phosphorus (2.5–4.5 mg/dL).

Statistical analysis

Demographic and clinical characteristics have been summarized as mean values (\pm standard deviation) or proportions. The continuous variables were also categorized as normal or abnormal depending on whether the specific value for a given subject fell inside or outside the normal limits. Depending on the type of variable the analyses were based on either parametric (ANOVA) or non-parametric (Chi-Square test) methods. The significance value was set at $p = 0.05$.

Results

The 82.6% of the sample was diagnosed with migraine, episodic (with or without aura) in 48% of the cases and chronic in the remaining 52%. Since CM was complicated by medication overuse (MOH) in the 91% of cases, the CM and MOH groups were lumped together in the CM-MOH group. The remaining

17.4% of the patients suffered from TTH, including episodic (71.4%) and chronic (28.5%) forms. Thus, a 3-category study variable (EM, CM-MOH, TTH) was taken into consideration for headache diagnosis.

Table 1 displays how the categorial variables were distributed in the 3 headache diagnostic groups.

Table 1
Demographic and Clinical data

	<i>All patients (n=80)</i>	<i>EM (n=32) 40</i>	<i>CM-MOH (n=34) 42.5%</i>	<i>TTH (n=14) 17.5</i>	<i>Chi-square ; p</i>
<i>Sex (females)</i>	92.5%	37.5%	38.8%	16.3%	0.16; p=0.923
<i>Work</i>					
<i>inside</i>	81.7%	26.8%	38%	16.9%	1.20; p=0.549
<i>outside</i>	18.3%	7%	10%	1.3%	
<i>Sport</i>					
<i>None</i>	67%	24%	33%	10.4%	2.478; p=0.649
<i>inside</i>	19.4%	9%	7.5%	3%	
<i>outside</i>	13.4%	3%	6%	4.5%	
<i>BMI</i>					
<i><18 kg/m²</i>	4.8%	0%	3.2%	1.6%	4.027; p=0.673
<i>18-24.99 kg/m²</i>	66.7%	28.6%	31.7%	6.4%	
<i>>25 kg/m²</i>	28.6%	9.5%	14.3%	4.8%	
<i>Dairy- free diet</i>					
<i>yes</i>	14%	4.2%	8.5%	1.4%	0.774; p=0.679
<i>no</i>	86%	31%	39.4%	15.5%	
<i>Comorbidities</i>					
<i>autoimmune diseases</i>	7.6%	2.5%	5%	0%	12.098; p=0.598
<i>diabetes mellitus</i>	1.3%	0%	1.3%	0%	
<i>fibromyalgia</i>	3.8%	2.5%	1.3%	3.8%	
<i>endometriosis and PCOS</i>	7.6%	3.8%	2.5%	1.3%	
<i>Menopause</i>					
<i>Yes</i>	36%	10.7%	21.3%	4%	5.620; p=0.060

<i>no</i>	64%	30.7%	20%	13.3%	
<i>Extracranial pain</i>					
<i>yes</i>	45%	10%	31%	4%	10.161; p=0.006
<i>no</i>	55%	26.8%	16.9%	11.3%	
<i>Allodynia</i>					
<i>yes</i>	47%	10.6%	33.3%	3%	10.40; p=0.005
<i>no</i>	53%	25.8%	16.7%	10.6%	
BMI = Body mass Index; EM= episodic migraine; TTH = tension type headache; CM-MOH = chronic migraine and medication overuse headache; POCS= polycystic ovary syndrome;					

The mean age of the CM-MOH group (51.8 years, standard deviation 11) was slightly but significantly (F04.46, p = 0.015) larger than those of the EM (43.1, 15.4) and of the TTH (41.6, 15.3) groups.

The 45% of the cephalalgic patients also had extracranial pain and 47% suffered from allodynia, and the occurrence of extracranial pain and allodynia was significantly larger in the CM-MOH than in the other groups. On the other hand, the number of subjects with extracranial pain and allodynia was not related to the co-occurrence of vit-D deficit as shown in Table 2.

Table 2
Association between headache type, pain extension and vitamin D levels

All patients (n = 80)			
ICHD-3 classification	VitD > 20 (n = 44)	VitD < 20 (n = 36)	Chi-square; p
<i>EM</i>	23 (52.3%)	9 (25%)	
<i>TTH</i>	9 (20.5%)	5 (13.9%)	
<i>CM-MOH</i>	12 (27.3%)	22 (61.1%)	9.504; p = 0.009
Extracranial pain			
<i>yes</i>	15 (47%)	17 (53.1%)	2.121; p = 0.145
<i>no</i>	25 (64.1%)	14 (36%)	
Allodynia			
<i>yes</i>	15 (48.4%)	16 (51.6%)	0.506; p = 0.477
<i>no</i>	20 (57.1%)	15 (43%)	
EM = episodic migraine; TTH = tension type headache; CM-MOH = chronic migraine and medication overuse headache; VitD = vitamin D.			

Table 3 shows the mean values and the out of normal range values (i.e. % of subjects falling outside the normal limits) of the continuous variables in the 3 headache diagnostic groups.

Table 3
Main biochemical parameters

<i>Variables</i>	<i>All patients (n = 80)</i>		<i>EM (n = 32)</i>		<i>CM-MOH (n = 34)</i>		<i>TTH (n = 14)</i>		<i>Chi-square; p</i>
	<i>OOR</i>	<i>mean ± SD</i>	<i>OOR</i>	<i>mean ± SD</i>	<i>OOR</i>	<i>mean ± SD</i>	<i>OOR</i>	<i>mean ± SD</i>	
VitD, ng/ml (< 20 ng/ml)	45%	20.3 ± 10.2	28.1%	19.9 ± 11.4	64.7%	20.1 ± 5.9	35.7%	21.7 ± 15.3	9.504; p = 0.009
Ca, mg/dl (vn 8.6–10.2)	3.8%	9.2 ± 1.3	3.1%	9.9 ± 0.6	5.9%	9 ± 1.9	0%	9.35 ± 0.2	1.008; p = 0.6
P, mg/dl (< 2.5)	1.3%	3.3 ± 0.3	3.1%	3.4 ± 0.4	0%	3.3 ± 0.3	0%	3.2 ± 0.3	1.519; p = 0.4
PTH, pg/ml (n 15–88)	9.8%	35 ± 26	8%	33.4 ± 19.6	10.7%	32.5 ± 25.1	12.5%	49 ± 45.4	0.183; p = 0.9
Folate, ng/ml (< 8.1)	27.3%	14.7 ± 10	21.4%	15 ± 10.8	33.3%	12.1 ± 5.3	27.3%	20.5 ± 17.1	3.099; p = 0.5
Vit B12, pg/ml (< 133)	11.4%	304 ± 142.8	20.7%	270.1 ± 145.3	6.9%	315.5 ± 141.8	0.0%	363.3 ± 125.2	4.594; p = 0.1
Homocysteine, μmol/l (> 12)	42%	12.7 ± 6.8	25%	12.8 ± 9.4	47.4%	12.1 ± 3.7	63.6%	13.4 ± 5.3	4.711; p = 0.095
Fe, μmol/dl (< 33)	15%	88.8 ± 41	15.4%	97.9 ± 43.3	19.2%	76.2 ± 41.8	0.0%	100.1 ± 19.4	1.780; p = 0.411
EM = episodic migraine; CM-MOH = chronic migraine and medication overuse headache; TTH = tension type headache; Ca = calcium; Fe = Iron; OOR = out of range; P = phosphate; VitB12 = Vitamin B12; VitD = Vitamin D; OOR = out of range.									

The analyses of variance (not shown in the Table) invariably proved that the mean values of the three groups were not statistically different. As for the occurrence of out of range values, the only significant comparison involved the vit D deficit that was larger in the CM-MOH than in the other two groups.

The season of enrollment, Table 4, did not significantly influence 25(OH)D concentrations. In detail, almost half of patients suffering from VitD deficit (45.8%) were enrolled during spring-summer season. Moreover, the mean value of vitD measured during the spring (20.09 pg/ml) and the one measured during autumn (20.7 pg/ml) were not statistically different (F = 0.69; p = 0.79).

Table 4

seasons of enrollment in the whole sample divided by vitamin D levels and headache categories.

Season	All (n = 80)	VitD > 20 ng/ml (n = 44)	VitD < 20 ng/ml (n = 36)	Chi-square; p	EM (n = 32)	CM-MOH (n = 34)	TTH (n = 14)	Chi-square; p
Aut-Wint n (%)	32 (40%)	18 (56.3%)	14 (43.8%)	0.034; p = 0.854	13 (40.6%)	13 (38.2%)	6 (42.9%)	0.097; p = 0.953
Spring-Sum n (%)	48 (60%)	26 (54.2%)	22 (45.8%)		19 (59.4%)	21 (61.8%)	8 (57.1%)	

Aut-Wint = Autumn-Winter; Spring-Sum = Spring-Summer; EM = episodic migraine; CM-MOH = chronic migraine and medication overuse headache; TTH = tension type headache; VitD = vitamin D. Data are reported as number (frequency).

Regarding the analyses of questionnaires, the mean FFS scale final score in the whole sample was 36 points. The subgroups suffering from EM and CM-MOH got higher scores at FFS (respectively 43 ± 15.1 and 41 ± 14.7 points) compared to TTH group (29.3 ± 14.4), but these differences were not statistically significant ($F = 0.98$; $p = 0.38$). According to the results of the HADS-A questionnaire, the three groups suffered from a mild state of anxiety (respectively: EM 10.5 ± 4.7 , CM-MOH 8.9 ± 4.5 and TTH 10 ± 2.6 points), again not statistically significant ($F = 0.44$, $p = 0.65$).

We compared the mean values and the occurrence of an abnormal values using the occurrence of vitD deficit as the explanatory variable, but all these comparisons did not prove to be significant. Finally, both the headache diagnosis and the occurrence of vit D deficit were non influenced by the ongoing pharmacological treatment (both prophylactic and abortive).

Discussion

The main result of our study was that the occurrence of vitD deficiency was more frequent in the CM-MOH than in the EM and TTH groups. This result, not influenced by the season of evaluation nor by the patient lifestyle or headache treatment, supported the hypothesis of a relationship between VitD status and the diagnosis of chronic migraine. The vitD deficiency was not significantly associated with any of the other variables that we considered, not to clinical features such as extracranial pain, allodynia and prophylactic treatment, nor to biological parameters. None of the other micronutrients tested proved to be different in the three diagnostic groups..

Our findings are in keeping with recent data that showed that poor vitD status was correlated to chronic pain (37) and with a high frequency of migraine episodes (38), but it is worth pointing out that the absence of correlation between VitD deficit and extracranial pain or allodynia, despite they frequently occur in MOH patients, suggests that they do not stem from the same pathophysiological mechanism of chronicization. The mechanisms underpinning migraine chronicity are not fully clarified, but they seem to be connected to a sensitization process acting at a peripheral level first, and at a central level afterwards (3). Central sensitization, driven by increased neuronal responsiveness and neuroinflammation, might perpetuate pain, even in the absence of any trigger (39). More recently, the role of the immune system along with neuropeptides release and blood flow modifications was also highlighted in mechanism of chronicization (39–41).

VitD mitigates inflammation by the reduction of pro-inflammatory mediators (such as interferon (IFN)-gamma, interleukin (IL)-1 beta, IL-6 and 17, tumor necrosis factor (TNF-alfa), favoring expansion of anti-inflammatory molecules (IL-4, IL-5, IL-10) (42). Notably, VitD reduces levels of the “nuclear factor kappa-light-chain-enhancer of activated B cells” (NF-kB), which is a pivotal agent in inflammation (43). Thus, VitD is supposed to counteract neuro-inflammation as well (44, 45).

An intervention study demonstrated that the reduction of pro-inflammatory cytokines by VitD supplementation was correlated to the improvement of musculoskeletal pain (46).

The regulation of oxidative balance is another potential mechanism of vitD anti-inflammatory action (17, 47, 48). As demonstrated by several trials, neurogenic inflammation in chronic migraine is mediated by oxygen free radicals (ROS) and nitric oxide (NO) concentrations (49–52). Togha and coworkers demonstrated that chronic migraineurs had lower total antioxidant non-enzymatic capacity and higher ROS levels than EM patients(50). Physiological VitD level decreases intracellular oxidative stress-related activities, up-regulating the expression of several genes implicated in mitochondrial activity, defense against oxidative burst and aging, and particularly of the nuclear factor erythroid-2(Nf-E2)-related factor and of Klotho (43, 53–57)

Obesity is a pro-inflammatory condition and bears the potential to intensify neurovascular inflammation. Previous reports observed that high BMI was correlated to severity and frequency of migraine episodes (58) -In our study this association was not confirmed but the small number of overweight people included (none suffering from obesity) could be a possible explanation. Moreover, in our patients the BMI and vit D deficiency were no related.

Conclusion

Although preliminary, these results support the active search for treatment strategies oriented to mitigate the neuroinflammatory response, as adjuvant agents in chronic migraine. VitD might have a rational use specially to treat those patients with initial features of migraine chronicity, as soon as signs of peripheral sensitization appear, exploiting its anti-inflammatory and tolerogenic properties rather than a direct antinociceptive effect.

Abbreviations

CM = chronic migraine; VitD = vitamin D; EM = episodic migraine; TTH = Tension Type Headache; MOH = Medication Overuse Headache; IFN = interferon; IL = interleukin; NF-Kb = nuclear factor Kappa-light-chain-enhancer of active B cells; NO = nitric oxide; ROS = oxygen free radicals; TNF = tumor necrosis factor ; FMS = fibromyalgia, BMI = Body Max Index; HADS-A = Hospital Anxiety and Depression Scale-Anxiety ; FSS = Fatigue Severity Scale

Declarations

Ethics approval and consent to participate.

not applicable. For this kind of study in which the data are collectable from the clinical records of the patients, we are not required to have a specific permission from the local ethical committee.

Consent for publication:

Not applicable.

Availability of data and materials:

our data is available upon reasonable request to the corresponding author.

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

All authors contributed in interpreting the data and writing the manuscript, read and approved the final manuscript, and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated, resolved, and the resolution documented in the literature. . VR, LPC, DG and PTD collected the data and performed the neurological and endocrinological assessment. MM and MV did the statistical analyses. All authors.

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