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REVIEW ARTICLE

Vitamin D in migraine headache: a comprehensive review on literature

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Abstract

Introduction As a primary headache, migraine has been established as the first leading disability cause worldwide in the subjects who aged less than 50 years. A variety of dietary supplements have been introduced for migraine complementary treatment. As an anti-inflammatory and antioxidant agent, vitamin D is one of these agents which has been of interest in recent years. Although higher prevalence of vitamin D deficiency/insufficiency has been highlighted among migraineurs compared to controls, there is not any consensus in prescribing vitamin D in clinical practice. Therefore, in the current review, in addition to observational and case-control studies, we also included clinical trials concerning the effects of vitamin D supplementation on migraine/headache.

Methods Based on a PubMed/MEDLINE and ScienceDirect database search, this review study includes published articles up to June 2019 concerning the association between migraine/headache and vitamin D status or supplementation.

Results The percentage of subjects with vitamin D deficiency and insufficiency among migraineurs and headache patients has been reported to vary between 45 and 100%. In a number of studies, vitamin D level was negatively correlated with frequency of headaches. The present findings show that supplementation with this vitamin in a dose of 1000–4000 IU/d could reduce the frequency of attacks in migraineurs.

Conclusion It seems a high proportion of migraine patients might suffer from vitamin D deficiency/insufficiency. Further, the current evidence shows that in addition to routine drug therapy, vitamin D administration might reduce the frequency of attacks in migraineurs. However, these results have yet to be confirmed.

Keywords 25-hydroxyvitamin D · Cholecalciferol · Headache · Immune function · Inflammation · Nociception · Pain

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Background

Migraine epidemiology and etiology

Current evidence shows migraine affects about 3–6% of pediatric and adolescents, 3.3–21.9% of adult women and 0.7–16.1% of men, with the highest burden on those age between 25 and 55 years. It is of note these age ranges are the most productive years of individuals lives. Therefore, the high economic and individual burden of migraine may be due to this reason. Additionally, the high rate of underdiagnosed and undertreated migraine cases is of serious concern because it augments the migraine related disability levels in patients [1–4].

Migraine attacks duration last between 4 and 72 h. Symptoms that are associated with migraine include unilateral and pulsatile headaches, nausea, vomiting, photo/phono/osmophobia [5]. There are two main types of migraine: chronic migraine ((CM) known as having more than 15 headache days/month) or episodic migraine ((EM) known as experiencing less than 15 headache days/month) are two main types of migraine headache that have been defined according to the frequency of headaches [6]. It has been estimated that only 20.2% of chronic migraineurs are diagnosed and accordingly properly treated. This can further exacerbate the individual functioning, family and societal interactions, and economic burden of migraine [7, 8].

It is assumed that both genetics and environmental factors, for example high sensitivity to sound, light, or some food items and influences of hormonal factors are involved in migraine attacks genesis. Female sex, low level of socioeconomic status or education, and head injury have been suggested as migraine unmodifiable risk factors while central sensitization, excess body weight, misuse of caffeine, smoking, having other types of headache simultaneously (e.g., tension type headache (TTH) or medication overuse headache (MOH)), high stress level, and snoring are known as modifiable risk factors. Also comorbidities of migraine headache such as cardiovascular disorders (such as Raynaud's disease, ischemic stroke, hypertension, mitral valve prolapse), psychiatric disorders (such as depression, anxiety, social phobias, and bipolar disorder), neurological disorders (such as epilepsy, Tourette's syndrome), sleep disorders, and allergy/asthma are involved in migraine progression [1, 9–14].

Migraine pathogenesis

It has been suggested that a migraine attack could be initiated following different internal and external triggers including stress, fluctuations in hormone levels, sensory overload, sleep disturbances, and the omission or lack of consumption of daily meals [15]. However, exact causes and pathophysiology of migraine headache has been poorly addressed in contrary to the efforts made on clarifying underlying mechanisms that are involved in migraine pain. Trigeminovascular pathway activation, cortical spreading depression (CSD), and inflammation, in addition to vascular dysfunction, are a number of the suggested mechanisms in migraine pathogenesis [16].

This type of primary headache is proposed to be a sign of changes in excitability state of the trigeminal pathway activating in the brain of those who have genetic susceptibility to develop migraine [15]. Pain signals from peripheral intracranial nociceptors that are activated via trigeminovascular pathway as well as CNS dysfunction in association with neuronal excitability modulation are among the most likely mechanisms initiating migraine [15]. Moreover, it is thought that CSD may either activate the trigeminal system to trigger the release of neuropeptides from the peripheral trigeminal afferents or may induce the mast cells to release pro-inflammatory mediators that can activate and sensitize the nociceptors causing an axon reflex to release the sensory peptides from the meningeal nociceptors. Thus, CSD could affect head pain initiation through causing the secretion of nitric oxide (NO), calcitonin gene-related peptide (CGRP), glutamate, a number of oxidative and inflammatory factors, and ions [16]. It is of note that inflammatory state in the meningeal vasculature also could initiate these responses [17].

In this regard, neuroinflammation is believed to probably influence the trigeminal nerves stimulation and vasoactive neuropeptides secretion that are associated with developing migraine [18–20]. Additionally, vasoactive neuropeptides such as CGRP and pituitary adenylate cyclase-activating polypeptide (PACAP) may induce trigeminovascular activation, arterial vasodilatation, and mast cells degranulation that all are thought to be involved in neuro-inflammatory state attributed to head pain in migraine [16, 17, 21–24]. On the other hand, secretion of CGRP and factors such as substance P (SP) and neurokinin A could also be provoked following central stimulation of the trigeminal system along with NO and serotonin release. Ultimately, these substances might accentuate inflammatory responses in trigeminovascular system specially through inducing vasodilation in the arteries and mast cells degranulation. Furthermore, oxidative stress that may be present in migraineurs could lead to destruction of integrity of cell membranes and nucleic acids, proteins, lipids, and extracellular components (e.g., collagens and proteoglycans) which additionally could aggregate CNS dysfunction in migraine suffers. This hypothesis is further confirmed by the studies detecting higher levels of neuroinflammatory factors including NO, CGRP, SP, histamine, vasoactive intestinal peptide (VIP), PACAP, neurokinin A, pro-inflammatory cytokines (including CRP, TNF-a, IL1-β, and IL-6), and biomarkers of oxidative stress (including malondialdehyde, thiobarbituric acid reactive substances, and total oxidant status) in migraineurs compared to healthy individuals [16, 17, 20–54].

Current treatment approaches in migraine

Migraine pharmacological therapy includes drugs that alleviate the acute attacks (such as triptans, ergot derivatives, and nonsteroidal anti-inflammatory drugs (NSAID)) in addition to prophylactic medications (including tricyclic antidepressants, serotonin–norepinephrine reuptake inhibitors (SNRIs), beta-blockers, calcium channel blockers, and anti-epileptic medications) [5, 8, 55–57]. However, few side effects of the current anti-migraine drugs (such as weight loss/gain, hypotension, decreased consciousness, sleepiness, and/or fatigue) could reduce patients' compliance. Thus, due to the fact that headache and especially migraine are often progressive disorders which could affect the patients throughout their lifetime and even disrupt their daily functioning, proper diagnosis and considering the best prophylactic agents for migraine treatment with the lowest side effects could substantially lead to migraine improvement. Therefore, new treatment strategies are required to be developed in order to enhance migraine attacks features, prevent its progression, and attenuate the migraine-related complications and disability as well as increase patients' quality of life. Using appropriate preventive/acute medications, eliminating/modifying the suggested risk factors of migraine development or progression through different strategies including applying dietary interventions, treating comorbidities and sleep disturbances are among the most important ways for overcoming the barriers in migraine treatment [1, 8, 55, 56, 58]. A variety of dietary supplements including magnesium, coenzymes Q10, vitamins B groups (B2, B3, B6, B9, and B12), melatonin, and omega 3 have been suggested to be effective in migraine prophylactic treatment [5, 59]. Vitamin D is one of these dietary agents which is of interest in relation to migraine. There are a number of review articles that address the role of dietary factors in headache which briefly described the association between vitamin D and headache [5, 59–62]. In two of the recent review articles [5, 59], a protective role for vitamin D in headache and migraine has been proposed. Another review paper [62] noted that although there was limited data on the effects of vitamin D in headache, supplementation with normally safe doses of this vitamin for children may help control headache. Few review articles that have focused specifically on the studies concerning the relationship between vitamin D and headache were published. According to the first one published in 2010, Prakesh et al. [63] claimed that serum concentration of vitamin D seems to be strongly correlated with the latitude. Therefore, they aimed to review the findings of studies in different regions in which headaches prevalence rate were reported. They finally showed that it seems to be a significant relationship between the latitude and prevalence rate of two main types of primary headaches (TTH and migraine). As such with increasing latitude, the headaches prevalence also raised. It was additionally stated that number of headache attacks elevated during autumn and winter despite lower number of attacks during summer. These findings match with seasonal and regional variations in vitamin D serum concentration [63]. However, the only systematic review on the contribution of vitamin D deficiency in migraine risk that included 7 studies (3 observational, 2 cross-sectional, and 2 case reports) failed to produce convincing evidence for a putative relationship between deficiency of vitamin D and migraine. The authors recommended to implement large randomized prospective trials and cross-sectional studies [64]. Additionally, in 2018, a systematic review and meta-analysis addressing the association between vitamin D levels and pain conditions included 5 observational studies on headache and vitamin D relationship in adults. They indicated that while patients with arthritis, muscle pain, and chronic widespread pain had significantly lower vitamin D concentrations, no significant differences were found among migraine and headache suffers and controls [65]. The authors, however, mentioned that these findings might be due to chance given that only 2 case-control studies and 3 cross-sectional analysis in headache patients were assessed [65]. Therefore, given these results are limited and inconclusive and also there are new publications [66–71] addressing vitamin D in relation to headache, an updated and comprehensive review article would be needed to further interpret the current evidence.

Based on the abovementioned issues, the aim of the current study is to focus on the following objectives: (1) describe cross-sectional studies that compare serum vitamin D levels of migraine/headache patients with healthy controls or examine the prevalence of vitamin D deficiency among patients, (2) describe clinical trials that investigate the effects of vitamin D supplementation on migraine/headache related features and complications, (3) explore the key findings of these studies according to the study type and quality, (4) speculate mechanisms through which vitamin D may influence migraine pathogenesis and progression, and (5) make recommendations for vitamin D monitoring and supplementation based on the current state of knowledge.

Vitamin D metabolism and biological functions

Vitamin D is found in two forms (D2 and D3). Vitamin D2 is derived from ultraviolet (UV) irradiation of the yeast sterol, ergosterol, that is naturally present in sun-exposed mushrooms while vitamin D3 is produced from 7-dehydrocholesterol in the skin following exposure to UV radiation and also is found in oil-rich fishes (e.g., salmon, mackerel, and herring) [72].

The first step of vitamin D metabolism takes place in the liver in which the enzyme vitamin D-25-hydroxylase (25-OHase) converts it to 25(OH)D. Then after in the kidney, 1-alpha-hydroxylase (an enzyme of the cytochrome P450 (CYP) system, CYP27B1) catalyzes 25(OH)D conversion to 1,25-(OH)2 D (or calcitriol, vitamin D biologically active form). Calcitriol binds to nuclear vitamin D receptor

(nVDR) that can be found in the kidneys (in which increases calcium reabsorption from the glomerular filtrate), small intestine (in which provokes absorption of calcium), and some of the other tissues. Furthermore, 1,25(OH)2D is also produced locally. Calcitriol might play a role in controlling up to 200 genes involved in various aspects of health and diseases [72, 73]. Likewise, it may be involved in a variety of biological pathways, such as suppression of cellular proliferation and stimulating terminal differentiation, angiogenesis inhibition, suppression of renin secretion, inducing production of cathelicidin by macrophage, and causing insulin secretion [72, 73].

In order to assess vitamin D status, the widely accepted approach is determining 25(OH)D serum concentration that could be a biomarker of both dietary vitamin D and the amount of vitamin D that is synthesized following UV radiation in the skin [73].

According to the Institute of Medicine (US) committee to review dietary reference intakes for vitamin D and calcium, the Recommended Dietary Allowances (RDAs) for vitamin D were as follows: 600 IU (15 mcg)/day for children and adults age 9–70 years and 800 IU (20 mcg)/day for adults age more than 70 years [19]. Sea fish and fish oils are good sources of vitamin D while dairy products and eggs contain smaller amount of this vitamin. It has been estimated that only around 20% of vitamin D recommended daily intake can be provided from dietary sources [74].

Inadequate exposure to sun, low dietary intake, impairment in the vitamin D synthesis or metabolism due to genetic factors, geographic-associated factors, malabsorption and GI disorders, chronic liver/kidney disorders, endocrine diseases (hyperparathyroidism, deficiency of growth hormone, diabetes mellitus), perinatal factors (such as maternal vitamin D deficiency in pregnancy, prematurity, and exclusively breastfed in 3–6 months of age) and some of the medications (including glucocorticoids, anticonvulsants (such as carbamazepine, phenytoin, phenobarbital, topiramate), antiretroviral and azole antifungal medications) are among the risk factors of vitamin D insufficiency/deficiency. Dark-skinned subjects, infants and adolescents, elderlies, and obese individuals, are at higher risk of vitamin D deficiency [71, 75–77].

The beneficial effects of vitamin D are beyond bone health and calcium metabolism. In this regard, a variety of epidemiological and clinical studies linked low levels of 25(OH)D to different health-related conditions including neurological and psychological disorders such as cognitive decline, Alzheimer diseases, depression, psychosis, autism, cardiovascular disorders, stroke, obesity and endocrine abnormalities, dysfunction of thyroid, autoimmune diseases, and cancer [71, 75, 78]. The high rate of vitamin D deficiency especially in developing countries, and the pivotal roles played by this vitamin in the brain and CNS function on the other hand, highlights the importance of vitamin D in relation to different disorders [79, 80].

Importantly, existing evidence recognized the role of this vitamin on certain brain functions. Calcitriol could affect on neuroplasticity, apoptosis, and gene expression of a variety of factors (e.g., neurotransmitters, neurotrophic and synaptic proteins) that all are related to the CNS function [81]. Vitamin D and its binding protein, 1-alpha-hydroxylase (certain enzyme in vitamin D metabolism), and VDR have been found in the CNS different region particularly the hypothalamus and substantia nigra [82]. These issues can further strengthen the effects of vitamin D on nervous system in health state and diseases (e.g., multiple sclerosis, Alzheimer disease, and migraine) [63, 81, 83, 84]. Indeed, vitamin D can modulate cellular oxidative stress level, intracellular calcium concentrations, immune system function and production of neurotrophic factor and also could inhibit the mechanisms result in neurodegeneration in cells. Thus, the protected role of this vitamin against neurodegenerative disorders could be justified [85].

Evidence acquisition

Based on a PubMed/MEDLINE and ScienceDirect database search, the current review study includes all published article during 2000 to 2019 concerning the association between migraine/headache and vitamin D. Papers on the effects of vitamin D for the acute or preventive treatment of migraine in children, adolescents, and adults (both men and women) were identified through a literature search. The fallowing terminology and keywords were applied: "25-hydroxyvitamin D," OR "vitamin D2," OR "vitamin D3," OR "ergosterol," OR "cholecalciferol" OR "calcitriol," AND "episodic migraine," OR "chronic migraine," OR "headache," OR "tension type headache," "epidemiology," OR "burden," OR "treatment strategies" AND "immune function," OR "inflammation," "endothelial function" OR "nociception," OR "pain." Each of the obtained articles was then cross-referenced to identify relevant studies. Studies were eligible to be included in the current review if they were written in the English language. All types of articles including observational studies ($n = 4$), cross-sectional studies ($n = 7$), case-control studies ($n = 5$), and clinical trials ($n = 6$) were included and reviewed.

Results and discussion

Observational, cross-sectional, and case-control studies

A number of researches have investigated 25(OH)D levels in the patients with headache or migraine that are described in Table 1. The majority of previous studies were observational, cross-sectional, and case-control studies. An inverse association between serum levels of this vitamin and headache has been shown in most of the previous studies [66–70, 86–93].

Table 1 An overview of the observational, cross-sectional, and case-control studies exploring vitamin D levels in association with headache

Study type/ season of study	Study population	Demographic data	Comorbidities	Outcome assessment	Key results/overall conclusion	Authors/publication year Ref. no
Retrospective observational study	Group A (migraineurs, $n = 165$) Group B (TTH suffers, $n = 116$) Group C: control ($n = 98$) enrolled between January 2015 and August 2018	Children aged 5–17 years (257 girls and 122 boys)	Obesity and excess body weight (between 31 and 59% had excess body weight)	Serum 25(OH)D levels: 15–20 ng/ml: insufficient < 15 ng/ml: deficient < 5 ng/ml: severely deficient	•No significant differences in mean 25(OH)D levels in group A (12.4 ng/ml), group B (13.5 ng/ml), group C (13.4 ng/ml). •Both A and B groups were vitamin D deficient •Mean 25(OH)D levels in girls suffering from both types of headaches (11.5 ng/ml), control girls (11.6 ng/ml). •Mean 25(OH)D levels in boys suffering from both types of headaches (15.7 ng/ml), control girls (16.8 ng/ml).•Mean 25(OH)D levels in girls suffering from primary headache < boys.•Vitamin D deficiency was present in girls and insufficiency was observed in boys.	Hanci, F., 2019 [1]
Case-control study	70 migraineurs 70 age- and sex-matched healthy individuals enrolled between April and September 2017	Mean (standard deviation, SD) of age in migraine group = 37 (9) (16 males and 54 females) Mean (SD) of age in control group = 37 (9) (19 males and 51 females)	None	Serum 25(OH)D < 20 ng/mL: deficient 20–29 ng/mL: insufficient 30–100 ng/mL: sufficient	•Mean serum 25(OH)D in migraineurs (30 ng/mL) < healthy subjects (43 ng/mL) •Percentage of subjects with vitamin D deficiency and insufficiency among migraineurs (53.7%) > controls (26.1%). •No significant differences in serum vitamin D levels of chronic migraineurs (31 ng/mL) as compared to episodic migraine patients (30 ng/mL) •No significant correlations between headache parameters (frequency or duration of attacks) and serum vitamin D •An inverse association between migraine and serum 25(OH)D (OR = 0.17; 95% CI = 0.04–0.64 comparing the highest serum 25(OH)D quartile with the lowest) after considering sex, age, body mass index, and use of anticonvulsant medications. • Each 5 ng/mL increment in serum 25(OH)D was accompanied by 22% decrease of migraine odds (OR = 0.78; 95% CI = 0.68–0.90). $P = .001$ •	Togha M, 2018 [2]
Retrospective observational study	157 migraineurs without control group enrolled between January 2016 and May 2017.	Mean (SD) of age = 37.0 (8.6) years (39 males and 118 females)	According to the mean (SD) score of Generalized Anxiety Disorder 7-item (GAD-7) (GAD-7) scale (6.1 (5.1)) of patients, they probably had mild anxiety.	Serum 25(OH)D level <20 ng/mL: deficient 20–29 ng/mL: insufficient >30 ng/mL: sufficient.	•Serum 25(OH)D level in patients = 15.9 ± 7.4 ng/mL. •77.0% (61.7% in autumn to 89.1% in spring) of migraineurs had vitamin D deficiency ($n = 121$) •94.9% of migraineurs had vitamin D insufficiency ($n = 149$) •The occurrence of more frequent monthly headache in migraine patients with vitamin D deficiency was 1.20 times (95% CI = 1.046–1.383) higher than in subjects without deficiency after considering age, sex, season (winter or spring and summer or autumn), subtype of migraine (chronic and episodic), depression, anxiety, and sleep quality.	Song, T. J., 2018 [3]
Retrospective case-control study	68 migraineurs	Migraineurs: girls ($n = 37$) mean (SD) of age = 12.2 (3.1)	No information.	Serum 25(OH)D < 20 ng/mL: deficient	•Mean serum 25-OH-D3 in migraine (17.3 ng/mL) and TTH patients (16.9 ng/mL) < controls (25.8 ng/mL).	Donmez, A 2018 [4]

Table 1 (continued)

Study type/ season of study	Study population	Demographic data	Comorbidities	Outcome assessment	Key results/overall conclusion	Authors/publication year Ref. no
	79 patients having tension-type headache (TTH)) 69 healthy controls) between November 2011 and June 2013	Boys ($n = 31$) mean (SD) of age = 10.8 (2.6) TTH: girls ($n = 47$) mean (SD) of age = 11.0 (3.0) Boys ($n = 32$) mean (SD) of age = 11.2 (2.8) Controls: girls ($n = 29$) mean (SD) of age = 10.5 (2.6) Boys ($n = 40$) mean (SD) of age = 10.6 (2.5)		20–29 ng/mL: insufficient 30–100 ng/mL: sufficient	•No significant differences in serum Ca, P, ALP and PTH levels between the headache patients and the controls. •Percentage of subjects with vitamin D deficiency (70.6%) and insufficiency among migraineurs (17.6%) < controls (%) and (%), respectively. •Percentage of subjects with vitamin D deficiency (67.2%) and insufficiency (17.7%) among patients with TTH (53.7%) < controls (%) and (%), respectively.	
Case-control study	•Group 1 = 100 patients (16 males, 84 females) having chronic migraine •Group 2 = 34 patients (6 males, 28 females) with episodic migraine •38 healthy controls (16 men, 22 women; enrolled from 2014 to 2017.	Mean (SD) of age in control group 39.8 (11.9) (6 males, 28 females) Mean (SD) of age in control group 47.6 (13.6) (16 males and 22 females)	None	Serum 25(OH)D < 20 ng/mL: deficient 20–30 ng/mL: insufficient 30 ng/mL <: sufficient	•A severe vitamin D deficiency among headache patients (especially in chronic migraine patients) compared with the healthy subjects. •Mean serum 25(OH)D (ng/mL) in chronic migraineurs (12.7) < episodic migraineurs (17.2) < healthy subjects (23.0) •A linear negative correlation between days with headache and serum 25(OH)D levels (Pearson correlation coefficient – 0.506)	Rapisarda, L 2018 [5]
Case-control study	100 patients with CTTH 100 healthy subjects were enrolled between February 2015 and October 2016	Mean (SD) of age in control group 35.63 (12.2) (37 males, 63 females) Mean (SD) of age in control group 36.86 (12.3) (39 Males and 61 Females)	None	Serum 25(OH)D < 20 ng/mL: deficient 20–29.9 ng/mL: insufficient > 30 ng/mL: sufficient	•A significant relationship between decreased serum 25(OHD) level and CTTH. (OR = 17.71 (95%CI = 7.1–47.6)). •Mean serum vitamin D level in CTTH group (14.7 ng/mL) < in controls 27.4 (14.7 ng/mL). •Percentage of subjects with vitamin D deficiency among CTTH patients (71%) > controls (25%). •Percentage of subjects with normal vitamin D among CTTH patients (6%) < controls (37%). •Duration of having headache among patients with less than 20 ng/mL (15.5 months) > patients with more than 20 ng/mL (11.2 months) •Having daily headaches among patients with less than 20 ng/mL (41%) > patients with more than 20 ng/mL (17%)	Prakash, S., 2017 [6]

Table 1 (continued)

Study type/ season of study	Study population	Demographic data	Comorbidities	Outcome assessment	Key results/overall conclusion	Authors/publication year Ref. no
					•Mean 25(OH) D levels in patients suffering from 'headache and musculoskeletal pain (12.8 ng/mL) < subjects with CTTH only (21.7 ng/mL). • Mean 25(OH) D levels in patients suffering from near daily headache (9.9 ng/mL) < others (17.1 ng/mL).	
Cross-sectional	population-based cohort study	A total of 2601 men of which 9.6% (250 men) had self-reported weekly or daily headaches (frequent headache) recruited through 1984–1989	aged 42–60 years old	•22–26% of studied subjects used cardiovascular medications •60–62% had •Hypertension•23–28% had coronary heart disease•2–3% had cancer4–7% had type 2 diabetes	Serum 25(OH)D level nmol/L	•Mean serum 25(OH) level in subjects with frequent headaches (38.3 nmol/L) < other participants (43.9 nmol/L) •An inverse association between frequent headaches and serum 25(OH)D (OR = 2.13, 95% CI = 1.42–3.18 comparing the lowest serum 25(OH)D quartile with the highest).
Virtanen, K. 2017 [7]						
Cross sectional study	Migraine without Aura (MWoA) ($n = 91$) Migraine with Aura (MWA) ($n = 32$) TTH ($n = 36$)	age between 5 and 18 year (67 males and 92 females)	No information.	Serum 25(OH)D level < 20 ng/ml: pathological. < 10 ng/ml severe hypovitaminosis.	•52.2% of the studied subjects ($n = 83$) had hypovitaminosis D in 12% had severe hypovitaminosis. •50% of MWoA, 56% of MWA and 44.4% of TTH suffers had hypovitaminosis D	Tozzi, El, 2016 [8]
Observational study	22 migraineurs without control group enrolled between April 2015 and June 2015.	Mean (SD) of age = 45.41 (11.22) (6 males and 16 females)	None	vitamin D levels (normal range = 30–100 ng/-ml).	•All 22 migraine patients were vitamin D deficient (mean vitamin D level = 13.05 ± 5.70). •No significant differences in serum vitamin D levels of chronic migraine and medication overuse headache patients (11.73 ng/mL) as compared to episodic migraine patients (15.86 ng/mL) •No significant correlations between headache frequency and serum vitamin D	Iannacchero, Rosario2015 [9]
Cross-sectional study	5938 subjects from National Health and Nutrition Examination	Mean (standdr error, SE) of age in those with	9–11% had coronary heart disease 3–3.6% had a history of stroke	Statin use Serum 25(OH)D levels nmol/l	•The prevalence of headache or migraine in the past 3 months among statin users ($n = 1069$) was 16.1% while it was about 20.9% among the participants did not consume a statin ($n = 4869$)	Buettner, C. 2015 [10]

Table 1 (continued)

Study type/ season of study	Study population	Demographic data	Comorbidities	Outcome assessment	Key results/overall conclusion	Authors/publication year Ref. no
	Survey (NHANES) were enrolled during 2001–2004.	25(OH)D < 57 nmol/l (n = 3537) = 56.5 (0.3) (55.1% female) Mean (SE) of age in those with 25(OH)D > 57 nmol/l (n = 2401 = 56.3 (0.3) (49.3% females)			•The prevalence of headache or migraine in the past 3 months among the subjects with 25(OH)D levels lower than 57 nmol/l (n = 3537) was 21.1% while it was about 19.1%, among the participants with 25(OH)D levels higher than 57 nmol/l (n = 2401) •Among statin users, the highest and lowest prevalence of headache or migraine was among subjects in the lowest and highest quartile of 25(OH)D levels, respectively. •A significant association between lower risk for severe headache or migraine and statin use in the subjects with 25(OH)D > 57 nmol/l (OR = 0.48;95% CI: 0.32, 0.71).	
Observational study	71 patients having chronic tension-type headache (CTTH) enrolled during January 2009 to November 2012.	Mean age = 38 years (39 female and 32 male).	•12 subjects had diabetes •7 subjects had Hypertension •34 subjects had self-reported depression •16 subjects had self-reported anxiety •All patients also had musculoskeletal pain	Serum 25(OH)D level > 20 ng/ml: normal < 20 ng/ml deficient	•52 CTTH patients (73%) were vitamin D deficient. •48–63% patients were likely to have osteomalacia. •Significant difference in mean 25(OH) D levels of patients who suffer from both musculoskeletal pain and headache (12.2 ng/ml) < those with only headaches (21.4 ng/ml). •Significant difference in mean 25(OH) D levels of subjects suffering from daily headache (9.8 ng/ml) < those with intermittent headaches (16.5 ng/ml)	Prakash, S., 2013 [11]
Cross-sectional prospective study	52 migraineurs 49 age- and sex-matched controls were enrolled in autumn 2012.	Mean (SD) of age in migraine group = 35.88 (9.10) (4 males and 48 females) Mean (SD) of age in control group = 34.24 (10.15) (7 males and 42 females)	None	•Serum 25(OH)D level • < 20 ng/mL: deficient •20–29 ng/mL: insufficient • > 30 ng/mL: sufficient •Vitamin D-binding protein (VDBP) •Vitamin D receptor (VDR)	•Mean serum 25(OH)D and VDR levels of migraineurs (38.8 ng/ml and 50.34 pg/ml, respectively) < controls (48.03 ng/ml and 53.91 pg/ml, respectively) •No difference in serum VDBP concentrations between cases and controls •No correlation between aura, headache attacks frequency, severity, duration and serum 25(OH)D, VDBP and VDR levels •12 migraineurs had vitamin D deficiency, 1 had insufficient levels and 39 migraineurs were vitamin D sufficient.	Celikbilek A, 2014 [12]
Case-control study	105 migraine patients 110 controls enrolled in the spring of 2011 from April to June	Mean (SD) of age in migraine group = 33.59 (0.97) (25 males and 80 females) Mean (SD) of age in control group 32.46 (0.91) (21 males and 89 females)	None	Serum 25(OH)D level < 20 ng/mL: deficient 20–29 ng/mL: insufficient > 30 ng/mL: sufficient	•No significant differences between mean serum 25(OH)D in migraineurs (13.55 ng/mL) and controls (13.19 ng/mL) •No relationship between headache severity and 25(OH)D levels. •Percentages of subjects with vitamin D deficiency and insufficiency among migraineurs were 45.7%, and 34.3%, respectively. •Percentage of subjects with vitamin D deficiency and insufficiency among controls were 51.8% and 30%, respectively.	Zandifar, A, 2014 [13]

Table 1 (continued)

Study type/ season of study	Study population	Demographic data	Comorbidities	Outcome assessment	Key results/overall conclusion	Authors/publication year Ref. no
					•No significant association between vitamin D deficiency severity and migraine. •No significant association between vitamin D level and headaches frequency, duration and symptoms	
Cross-sectional study	Seventy-six migraine patients (72.4% women and 27.6% men) aged 10–61 years were enrolled in autumn 2012	Mean (SD) of age = 33.1 (11.1) (55 female and 21 male)	No information	Serum levels of vitamin D, 25(OH) D3: < 12 ng/ml: deficient 12–30 ng/ml: insufficient > 30: sufficient	•Among migraineurs, percentage of subjects with vitamin D deficiency, insufficiency and sufficiency were as follows: 13.2%, 68.4%, and 18.4%, respectively. •Percentage of subjects with normal vitamin D among migraineurs (6%) < controls (37%). •No significant correlation between serum vitamin D concentration and severity of migraine. •A significant direct association between serum vitamin D concentration and headache diary results	Mottaghi, T., 2013 [14]
Cross sectional study	11,614 participants of the sixth survey of Tromsø study in 2007–2008. 248 subjects among non-smokers and 74 subjects among smokers had migraine. 2906 patients in non-smokers group and 833 patients in smokers group suffered from non-migraine headaches.	5492 males, 6122 females Mean age about 55 to 58 years	Numbers of chronic diseases including self-reported asthma, diabetes, hypertension, and stroke were 0.44 among non-smokers and 0.37 among smokers.	Serum 25(OH)D ng/mL	•Among non-smokers: mean serum 25(OH)D (nmol/L) of migraineurs (n = 248, 53.0) and non-migraine headache suffers (n = 2906, 53.5) < headache free subjects (n = 6121, 55.8) •No significant differences in serum 25 (OH)D levels of the studied groups among non-smokers •An inverse association between non-migraine headache and serum 25(OH)D (OR = 1.20; 95% CI = 1.04–1.39) comparing the lowest serum 25(OH)D quartile with the highest) among nonsmokers. •No significant relationship between migraine and serum 25(OH)D in the studied population.	Kjaergaard, M. 2012 [15]
Cross-sectional study	509 subjects suffering from local pain, fatigue and general pain 63 patients suffering from headache enrolled during 2005–2007,	166 male and 406 female	No information.	Serum 25(OH)D level < 50 nmol/L defined as hypovitaminosis D	•Mean 25(OH)D level in patients with headaches < patients suffering from musculoskeletal pain, or fatigue. •Hypovitaminosis D was present in more than 50% of studded population. •50 subjects out of 334 (15%) with hypovitaminosis D reported headache, in comparison with 13 subjects out of 238 (5%) among those with adequate 25(OH)D level •An inverse association between headache and hypovitaminosis D (OR = 2.6) after considering gender, season, geographic region of origin, and age.	Knutsen, K 2010 [16]

Moreover, the percentage of subjects with vitamin D deficiency and insufficiency among migraineurs and headache patients has been reported to vary between 45 and 100% [67, 68, 70, 86, 94].

According to the research by Knutsen et al. in 2010, patients with headache were found to have the lowest level of serum vitamin D among subjects suffering from different types of pain related disorders including musculoskeletal pain and fatigue [87]. Interestingly, given vitamin D deficiency has been linked to both bones osteomalacia (musculoskeletal pain) and chronic headache, Prakash et al. (2013) hypothesized that skull bone osteomalacia might play a role in head pain generation [89]. Also in another research (Prakash et al. (2017)), it has been reported that insufficiency of vitamin D was accompanied by higher risk of chronic TTH [92]. Regarding the studies on pediatrics, there was found that in comparison to controls, vitamin D deficiency was more prevalent among children with TTH and migraine [66, 93]. These findings were especially prominent in in those with migraine without aura [93] and girls [66].

A number of the previous studies also investigated serum vitamin D status of migraine patients. The findings of the sixth survey of Tromsø Study (Tromsø6) on 11,614 subjects, revealed that although there was no significant relationship between migraine and serum vitamin D levels, non-migraine headache risk was negatively associated to serum 25(OH)D serum levels [95]. Similarly, Zandifar et al. [94] failed to display any significant differences in the level of 25(OH)D of migraineurs compared to controls [94]. The results of other studies addressing vitamin D levels in migraineurs, however, contradict these conclusions. Interestingly, in the study by Buettner et al. in 2015 [91], a significant interaction was noted between severe headache prevalence with statin consumption and serum vitamin D levels. As such it was shown that statin consumption in the subjects with serum vitamin D concentration more than 57 nmol/l was significantly related to decreased odds of severe headache/ migraine [91]. In a case-control study conducted by Togha et al. in 2018 on 70 migraineurs and 70 healthy individuals, each 5 ng/mL elevation in serum vitamin D level was shown to be associated with 22% reduced odds of migraine headache [67]. It is worth noting that based on the findings of Celikbilek et al. (2014), in addition to serum 25(OH)D levels, concentration of VDR was also found to be lower among migraine patients; while serum levels of vitamin D binding protein did not differ as compared to controls [90].

Whereas the majority of studies did not find significant correlations between serum vitamin D and headache characteristics [67, 86, 90, 94], Rapisarda et al. showed that with increasing number of days with headache, vitamin D serum concentration decreased (Pearson correlation coefficient—0.506; $p < 0.001$) [70]. Besides, Song et al. [68] found that in comparison to migraine patients without vitamin D deficiency, the risk of experiencing higher number of headaches per month was 1.2-fold greater among those with deficiency of this vitamin [68]. Moreover, in 2012, Mottaghi et al. revealed a significant positive association between serum vitamin D and headache diary results in 76 migraineurs while no relationship was evident with severity of migraine [96]. Additionally, it has been suggested that mean 25(OH) D levels in patients suffering from near daily headache may be lower than others [92]. Also, Prakash et al. [89] showed a significantly lower 25(OH) D levels of subjects suffering from daily headache than those with intermittent headaches [89]. Besides, in another study on 2601 men of which 250 patients had frequent headaches, it was found that lower level of vitamin D is related to the 113% increased risk of experiencing daily or weekly headaches [88].

Clinical trials

Table 2 presents the details of clinical trials of vitamin D supplementation in headache/migraine patients. Up to our knowledge, to date there were 4 studies [71, 97–99] on vitamin D administration in headache patients of which 3 researches have been conducted on migraineurs.

Mottaghi et al. observed that 10-week supplementation with 50000 IU/week vitamin D resulted in partially significant reduction of number of headache attacks and improved headache diary results in migraineurs, while no significant effect was noted on CRP levels [98]. These results were also confirmed by the most recent double-blinded randomized controlled trial [71]. In this study, Gazerani et al. explored the effects of 4000 IU/day (100 μg/day) vitamin D vs. placebo after 6 months of treatment in 48 migraineurs. Interestingly, significant improvement in the frequency of headache days was noted in the intervention group. Moreover, patients in the intervention arm reported higher responder rate (≥ 50% enhancement in number of migraine attacks), though no significant changes in intensity of head pain and thresholds of pressure pain were observed. None of the patients had any adverse reactions [71]. Moreover, in a clinical trial performed by Buettner et.al. in 2015 [97], higher decrease in the migraine days frequency was recorded among those received simvastatin 20 mg + vitamin D3 1000IU twice daily compared to placebo [97].

Results from the only interventional study in migraine children done so far are also promising. Coadministration of amitriptyline and vitamin D (400, 800, or 5000 IU/day) on 53 pediatric migraine patients during 6-month enhanced migraine attacks frequency [99].

In addition, there are studies which assessed headache status after vitamin D supplementation as a secondary outcome. Yilmaz et al. exhibited decreases in frequency and severity of headaches following administration of 50000 IU/week vitamin D + 1000 mg/day elemental calcium for 3 months in 20

Table 2 An overview of clinical trials of vitamin D supplementation in headache/migraine patients

Study type	Study population/ time of study	Comorbidities	Demographic data, dose, duration	Results In the end of the study in treatment group	Authors/publication year Ref. No
Randomized, double-blind, placebo-controlled parallel trial	48 migraineurs enrolled from 2012 to2016	None	24-week (including 4-week baseline) of: supplementation with 100 μg vitamin D3/day ($n = 24$, mean (SD) of age = 45.5 (43.7), 18 women and 6 men) or placebo ($n = 24$, mean (SD) of age = 43.7 (10.2), 18 women and 6 men).	•Higher responder rates were noted following supplementation with vitamin D. •A significant improvement in the attack frequency (from 3.00 to 1.29) and number of migraine days (from 6.25 to 3.28) from baseline to week 24 following supplementation while no significant changes in attacks severity •No significant change was observed either attack frequency or severity or migraine days in placebo arm •No significant changes in migraine-associated symptoms or HIT-6 scores and serum levels of 1,25(OH)2D levels following supplementation.	Gazerani, P., 2019 [17]
Randomized placebo controlled trial	57 episodic migraineurs September 2010–March 2013.	Seasonal allergies: 10 and 14% Depression: 6 and 8% Anxiety: 4 and 6% Asthma: 2 and 4% Raynaud's syndrome: 1 and 3% in the active and placebo groups.	24-week trial of: simvastatin 20 mg twice per day +vitamin D3 1000IU twice per day ($n = 28$, mean age = 40, 27 females and 1 males) placebo ($n = 29$, mean age = 29, 25 females and 4 males)	•Higher decrease in the migraine days frequency among simvastatin+ vitamin D3 than placebo group Change from the baseline to the weeks 13–24 of intervention: active arm: − 9.0 (IQR = − 13–5) days placebo arm: + 3.0 (IQR − 1.0 − +5.0) days •About 25–29% of migraineurs in the simvastatin+ vitamin D3 group had 50% decrease in their migraine days frequency while only 1 patient in the placebo arm had this level of decrease	Buettner, C, 2016 [18]
Pre-post trial	58 patients with nonspecific chronic widespread musculoskeletal pain (CWP)	Fibromyalgia (FM) and deficiency of vitamin D (< 25 ng/mL)	3-month supplementation with 50 000 IU/week vitamin D3 ($n = 58$, mean (SD) of age = 36.9 (9.2), 52 females and 6 males)	•29 patients had headache at baseline •About 69% ($n = 20$) of patients with headache had 50% decrease in their migraine days frequency following supplementation •Enhancements of serum 25(OH)D levels, pain, asthenia, quality of life, depression status, and headache were reported following supplementation	Yilmaz, R, 2016 [19]
Randomized, double-blind clinical placebo controlled trial	65 migraineurs in autumn 2012.	No information	10-week weekly supplementation with: 50,000 IU vitamin D3 ($n = 33$, 25 females and 8 males, mean (SD) of age = 32.7 (10.6)) or placebo ($n = 32$, 22 females and 10 males, mean (SD) of age = 33.9 (11.6))	•About 15.4% of studied patients were vitamin D deficient, 66.1% were insufficient and 18.5% had normal levels. •No significant differences in mean changes of migraine severity or duration in the intervention and control group after the study •Mean migraine frequency in the intervention group from baseline to the end of study (from 8.4 to 5.9) < control group (from 8 to 7.0): $P = 0.06$	Mottaghi, T, 2015 [20]
Randomized, double-blinded, placebo--controlled, parallel-group trial	251 subjects were followed up through the trial between January and June 2011.	musculoskeletal pain and headache	16-week daily supplementation with: 25 μg ($n = 75$, 58 females, 26 males, mean age = 35–40 years)	•63% (157 of 251) of the studied individuals experienced headaches during around a month before the study initiation. •Significant elevation in serum 25(OH)D3 in 25-μg/d D3 group (from 27 nmol/L to 52 nmol/L) and 10-μg/d D3	Knutsen, K. V., 2014, [21]

Table 2 (continued)

Study type	Study population/ time of study	Comorbidities	Demographic data, dose, duration	Results In the end of the study in treatment group	Authors/publication year Ref. No
			10 μg vitamin D3 ($n = 69$, 61 females, 24 males, mean age = 36–40 years) placebo ($n = 71$, 63 females, 19 males, mean age = 38–39 years)	group (from 27 nmol/L to 43 nmol/L) while no changes observed in the placebo group relative to baseline. •Although the number of subjects having pain or headache or severity of pain and headache decreased in both groups, no significant differences in the levels of pain indicators, pain sites, headache and pain severity, or analgesic medications consumption (pain killers), in the groups supplemented with vitamin D compared to placebo	
Prospective trial	53 pediatric migraineurs between June 2011 and June 2012.	None	6-month follow-up: Group 1 patients with 25(OH)D > 20 ng/mL: normal, received only amitriptyline therapy ($n = 13$, 3 females and 10 males, mean (SD) of age = 11.8 (0.58)) Group 2 patients with 25(OH)D > 20 ng/mL: normal, received vitamin D 400 IU/day + amitriptyline ($n = 13$, 5 females and 8 males, mean (SD) of age = 12 (0.69)) Group 3 patients with 25(OH)D 15–20 ng/mL: insufficient, received vitamin D 800 IU/day + amitriptyline ($n = 14$, 9 females and 5 males, mean (SD) of age = 12.7 (0.62)) Group 4 patients with 25(OH)D < 15 ng/mL deficient, received vitamin D 5000 IU/day + amitriptyline (n = 13, 7 females and 6 males, mean (SD) of age = 12.3 (0.52))	•Significant within group decrease in the mean attack frequency relative to baseline and in comparison with group 1: Group 1 (baseline 25(OH)D levels = 32.4): 7 to 3 Group 2 (baseline 25(OH)D levels = 28.1): 6.8 to 1.76 Group 3 (baseline 25(OH)D levels = 17.2): 7.3 to 2.14 Group 4 (baseline 25(OH)D levels = 10.9): 7.2 to 1.15 •There were significant increases in serum 25(OH)D levels in the patients in groups 3 and 4 (25.6 and 22.3 ng/mL, respectively)	Cayir, A., 2014 (22)

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out of 29 patients [100]. However, a randomized double-blind controlled trial conducted by Knutsen et al. in 2014 failed to show any significant improvement in VAS and the Headache Impact Test (HIT-6) score after about 4-month supplementation with vitamin D (400 (10 Mg/day) or 1000 (25 Mg/day) IU/day) vs placebo [101]. It however seems that the assigned diagnosis of headache was nonspecific in that study and based on patient complaint of having headache [101].

Vitamin D and headache: a mechanistic overview

Vitamin D and pain

Specifically, vitamin D deficiency has been linked to different pain-related disorders though no causal association has been found. Clinical trials have observed a positive pain relieving effect of this vitamin especially in those with serum 25(OH)D levels less than 30 nmol/L [102–106]. In other studies, an increased prevalence of hypovitaminosis D deficiency was also noted in patients suffer from persistent, nonspecific pain, musculoskeletal pain situations, and rheumatologic diseases [104, 107]. Anti-inflammatory effects of calcitriol, controlling T helper cells, acting as a neuroactive steroid, inhibition of NO synthase, suppression of PGE2 are among the proposed mechanisms for pain killing action of vitamin D [102, 107].

Vitamin D, immune system regulation, and inflammation

It has been confirmed that vitamin D level is reversely correlated to the inflammatory state. Previous evidence showed that the levels of proinflammatory/oxidative agents, for instance, hs-CRP, CRP, IFN-g, IL-1β, IL-6, TNF-α, IL-17, MDA have been reduced subsequent to supplementation with this vitamin [104, 108–113]; on the contrary, vitamin D administration has been reported to rise the secretion of anti-inflammatory factors (e.g., IL-4, IL-5, and IL-10) and total antioxidant capacity [81, 112, 113].

The expression of nVDR in immune and inflammatory cells' further proves the roles of vitamin D3 in regulating activation, proliferation, and differentiation of these cells [73, 81]. Moreover, the certain metabolite of this vitamin (1,25-dihydroxycholecalciferol) has been reported to be produced by stimulated macrophages. Thus, the other pathways that may contribute sufficient levels of vitamin D to inflammation suppression may include cyclooxygenase-2 (COX-2) inhibition and therefore inhibiting prostaglandin E2 (PGE2) production [81, 104, 114]. Additionally, inhibiting the adaptive immune system, suppressing proliferation of Th1 and Th17 cells, and preventing release of pro-inflammatory cytokines are among the other effects of this vitamin on immune system function. These events could shift the balance of T helper cells to Th2 and Treg (regulatory T cells) through increasing IL-4 and transforming growth factor-β (TGF-β) secretion [81, 104, 114]. It is noteworthy that dysregulation in the Th1/Th2 balance might be contributed to migraine nociception [20]. The effect of TGF-β in reducing pro-inflammatory mediators secretion (for instance, TNF-α, interferon-γ (IFN-γ), and IL-1) has also been supported by prior studies [81, 104, 114]. Besides, nuclear factor-κB (NF-κB) plays a key role in regulating pro-inflammatory cytokines secretion and modulating immune responses. NF-κB is suppressed when it binds to its inhibitory protein, known as inhibitor of κB protein (IκB). Vitamin D may suppress the activation of 65 unit of NF-kB complex via increasing IkBα expression and influencing on a variety of factors involved in NF-κB pathway. Thereby this vitamin can protect against production of pro-inflammatory mediators [73, 81].

Vitamin D is also related to oxidative stress modulation through regulating the rate of oxygen consumption, affecting the mitochondrial function. It has been indicated that Vitamin D deficiency is attributed to lower concentrations of VDR and higher levels of oxidative stress [84, 115].

Vitamin D and NO

The roles that played by NO as a vasodilator factor in initiating migraine attacks could be attributed to its ability in activating NO/cyclic guanosine monophosphate (cGMP) signaling pathway in addition to elevating CGRP release that finally could stimulate nociceptive neurons particularly in trigeminovascular system. In addition, NO may increase the production of SP in the perivascular nociceptors that could augment the inflammation level in the CNS along with CGRP during pain genesis [23, 48, 116]. This neurotransmitter is believed to affect the nociceptive process through playing a role in central sensitization development in dorsal horn of the spinal cord [117].

On the other hand, higher levels of NO have been reported to be associated with lower serum 25(OH)D concentration. This inverse association could also endorse the effects of vitamin D on endothelial function and cardiovascular system [118]. Besides, it has been proposed that iNOS may induce neuronal damage and death through catalyzing synthesis of NO. Over-synthesis of NO could cause neuronal damage via inhibiting cytochrome oxidases activities in mitochondria [85], whereas 48-h administration of vitamin D in hippocampal neuron cultures resulted in lower expression of iNOS mRNA in comparison with control group that finally lead to suppressing oxidative stress induced by iNOS [85]. It has been additionally shown that 1,25(OH)2D3 may control NO transcription in endothelium and therefore modulate vascular function [104, 119].

Furthermore, 1,25(OH)2D3 may also be important in the regulation of glutathione (GSH) metabolism through maintaining the activity of the certain enzyme in this process

(gamma-glutamyl transpeptidase (GGT)). It is of note that GSH may be involved in the procedure of eliminating nitrogen and oxygen reactive species (including NO) in astrocytes [117, 120].

Other likely mechanism

The other likely explanation for beneficiary effects of vitamin D in migraine could be related to direct relationship between 25(OH)D serum concentrations and magnesium (Mg) levels [121, 122]. The clinical significance of this association can be appreciated by considering the fact that depletion of Mg may be contributed to migraine pain pathogenesis [123, 124]. According to the existence of vitamin D receptor in the brain tissues and central nervous system, it has been proposed that vitamin D may play a role in the neuronal development and biosynthesis of neurotransmitters and neurotrophic agents, such as nerve growth factor (NGF), a necessary molecule play a role in hippocampal and cortical neurons survival [75]. Moreover, this vitamin has been related to widespread and regional alterations in neurotransmitter levels (for example glutamine, noradrenaline, dopamine, and serotonin) [75]. In addition, in a cross-sectional research conducted by Motaghi et al., the relationship between migraine and two gene polymorphisms of VDR (including TaqI f/F and FokI t/T) was evaluated. They studied 103 migraineurs and 100 healthy controls and found that both heterozygote genotypes were significantly more prevalent in migraine group in control arm (for TaqI, OR = 1.81 (95% CI = 1.03–3.18) and for FokI OR = 2.91 (95% CI = 1.47–5.77) [125].

Contribution of vitamin D in migraine pathogenesis: summary

It has been suggested that low vitamin D levels could affect the probable pathways contributed in migraine pathophysiology via a variety of mechanisms. As mentioned earlier, CSD as well as inflammatory state in the meningeal vasculature could affect head pain initiation [16, 17]. Additionally, vasoactive neuropeptides such as CGRP and PACAP may induce trigeminovascular activation, arterial vasodilatation, and mast cells degranulation that all are thought to be involved in neuroinflammatory state attributed to head pain in migraine [16, 17, 21–24]. Higher levels of neuro-inflammatory factors and biomarkers of oxidative stress in migraineurs compared to healthy individuals confirm this hypothesis [16, 17, 20–54]. Therefore, augmented inflammatory status and immune system dysfunction are among the mechanisms that seem to contribute in pain sensitization in migraine [20, 47–52]. On the other hand, it has been demonstrated that vitamin D as an essential neuro-steroid vitamin has antioxidant and anti-inflammatory features [75]. Thus, this anti-inflammatory hormone could affect immune responses, function of the endothelial system, and cell proliferation. It is of note that deficiency of vitamin D could influence the inflammatory processes in the brain which results in predisposing the brain to these pathophysiological events [75, 126, 127]. Importantly, the presence of vitamin D and its metabolites in hypothalamus with regard to the pivotal role played by this region in migraine pathophysiology [82], make this vitamin more significant in migraine. Therefore, it can be speculated that correcting vitamin D deficiency can help protect against migraine development/progression. On the other hand, considering the fact that few drugs have been identified to be fully effective in migraine treatment, more investigations into its pathophysiology are required. Along with advancing our understanding of pathophysiological mechanism of migraine headache, more specific agents to protect against these mechanisms would be developed [128, 129]. Thus, it seems that vitamin D can be applied as a therapeutic agent in combination with existing treatments for migraine .

Expert opinion for vitamin D recommendation in migraine

According to new evidence, prescribing daily vitamin D in lower daily doses might be more effective than high-doses which prescribed on weekly or monthly basis. Moreover, vitamin D3 2000IU/day could be used as maintenance therapy [130, 131]. On the other hand, the same dose might affect immune system and cytokines release from T helper cells that may play a role in migraine pathogenesis [130, 131]. In addition, daily vitamin D3 upper limit is up to 4000 IU even in subjects with normal serum 25(OH)D levels is thought to be safe [72, 132, 133]. Therefore, it seems that supplementation with daily vitamin D in a dose of 2000-4000 IU might improve migraine features though more studies are necessary to determine the proper doses of this vitamin D for complementary therapy in migraine. Importantly, obese individuals (body mass index (BMI) > 30 kg/m^2, elderlies, the subjects with inadequate sunlight exposure or a sedentary lifestyle, dark-skinned people, those who consume glucocorticoids, anticonvulsants, antifungals, and anti AIDS/HIV drugs, and patients with malabsorption disorders, liver or kidney diseases, or primary hyperparathyroidism who are at an increased risk for developing hypovitaminosis D [72] should be paid more attention in the clinical practice.

Conclusion

In sum, as it seems a high proportion of migraine patients might suffer from vitamin D deficiency/insufficiency, urgent action by health care providers is encouraging. Furthermore, vitamin D level in headache patients was negatively correlated with frequency of headache. However, large sample size

prospective cohort studies should be performed in order to clarify the association between headache characteristics including frequency, intensity and duration, and serum 25(OH)D status. Further, the present findings regarding vitamin D supplementation in migraineurs indicate that in addition to routine drug therapy, vitamin D administration might reduce the frequency of attacks in migraineurs. From a mechanistic point of view, it can be speculated that correcting vitamin D deficiency can help protect against migraine development/progression. Also, it seems that vitamin D can be applied as a therapeutic agent in combination with existing treatments for migraine. However, these results have yet to be confirmed. Well-designed randomized controlled trials are suggested to explore vitamin D clinical and histological efficacy on migraine/headache features.

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Compliance with ethical standards

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