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The role of vitamin D in migraine, from mechanism to therapy: literature review

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ABSTRACT

Migraine is a neurological condition that is the third highest cause of disability in the population under 50 years old. The Increasing incidence of migraine will affect the quality of life and increase the financial burden on the patient. Vitamin D is one of the supplementation agents that is thought to be associated with headaches and has anti-inflammatory and antioxidant effects. There is an increasing prevalence of vitamin D deficiency in migraine patients but there is no consensus regarding the provision of vitamin D supplementation as a complementary therapy in migraine. This article aims to explain the role of vitamin D in the mechanism of headache, especially migraine, and vitamin D supplementation therapy as a complementary therapy in migraine. Vitamin D is thought to play a role in the pathogenesis of headache through several mechanisms, namely as an anti-inflammatory effect, regulates the immune system, reduces nitric oxide (NO) levels, suppresses prostaglandin synthesis, and is associated with changes in several neurotransmitters such as glutamine, noradrenaline, dopamine, and serotonin. Several studies have reported that vitamin D supplementation in patients with migraine can improve the frequency of headache attacks. Most migraine patients can experience vitamin D deficiency. Vitamin D supplementation is also thought to reduce the frequency of headache attacks in migraine patients. However, further research is still needed to confirm these results.

Keywords: vitamin D, migraine, complementary therapy

INTRODUCTION

Migraine is a neurological condition that causes disability and affects the socioeconomic function and quality of life of the patient. Migraine is also the third leading cause of disability in both men and women under 50 years old [1]. Migraine prevalence ranges from 15-18% worldwide annually. This condition causes a global economic burden that reaches 19.6 billion dollars in America and 27 billion euros in Europe every year [2]. The prevalence ratio in women and men varies with age, in the age range of 12-17 years migraine is reported to occur more in men with a 1.5:1 ratio. At the age of 18-29 years, migraines were reported to occur more in women with a ratio of 3.25:1 [3].

The characteristic symptom of migraine is a headache lasting about 4 hours to 72 hours, with unilateral location, pulsating quality of moderate/severe intensity, and may be followed by nausea and/or vomiting as well as photophobia and phonophobia. These headaches are exacerbated by doing routine activities such as walking and climbing stairs [4]. When distinguished from the frequency and duration, Migraine is divided into two main types, they are chronic migraine and episodic migraine. Migraine is categorized as chronic migraine if the headache occurs 15 or more days per month for more than 3 months, at least 8 days per month [4]. Only about 20.2% of chronic migraines are diagnosed correctly and receive adequate therapy. This will aggravate the exacerbation and affect the socioeconomic function and social interaction of the patient [5].

Genetic and environmental factors are thought to play a role in the onset of migraines. The non-modifiable risk factors were female gender, low socioeconomic status and education, and head injury. Mod-

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ifiable risk factors include being overweight, excessive caffeine consumption, smoking, and high stress levels. In addition, migraine comorbidities such as cardiovascular disease (such as Raynaud's disease, ischemic stroke, hypertension), psychiatric disorders (such as depression, anxiety, bipolar), neurological disorders, sleep disorders, and allergies/asthma contribute to migraine progression [6].

MIGRAINE PATHOPHYSIOLOGY

The incidence of migraine attacks is thought to be triggered by internal and external factors such as stress, hormonal fluctuations, excessive sensory sensitivity, sleep disturbances, and dietary factors. However, the exact cause and pathophysiology of migraine are not fully understood. Trigeminovascular pathway activation, Cortical Spreading Depression (CSD), neuroinflammation, and vascular dysfunction are thought to be mechanisms in the pathogenesis of migraine [7].

This primary headache is thought to occur as a sign of altered flexibility from activation of the trigeminal pathway in the brain of patients with a genetic predisposition to migraine [8]. Pain signals from peripheral intracranial nociceptors activated by the trigeminovascular pathway and central nervous system dysfunction are associated with modulation of neuronal excitability. The CSD theory is thought to activate the trigeminal system by stimulating neuropeptide release from peripheral trigeminal afferents or by stimulating mast cells to release proinflammatory mediators that activate and sensitize nociceptors. CSD is a wave that produces spontaneous suppression of cortical neuronal activity and spreads over the gray matter at an average rate of 2-5 mm/min. This can increase the activation of trigeminovascular pathways and neuroreceptors in the superficial lamina and trigeminocervical complex [8]. The depolarizing activity of this CSD wave also triggers headaches by causing secretion of nitric oxide (NO), prostaglandins (PG), calcitonin gene-related peptide (CGRP), glutamate, and other inflammatory, and oxidative factors [9].

Nitric oxide and prostaglandins are thought to play a role in pain modulation through several mechanisms. Under inflammatory conditions NO and PG are produced in large quantities, which modulate neuronal activity and mediate nociceptive information processing in the central nervous system. NO can play a direct role in cyclooxygenase (COX) expression and prostaglandin biosynthesis. COX-2 can increase the production of prostaglandin E2 (PGE2) in the central nervous system and contribute to the severity of the pain response in inflammatory pain. These inflammatory factors can activate trigeminal dura afferents and brainstem neurons via meningeal input. Hyperproduction of NO and PGE2 plays a role in the neurovascular modification that triggers migraine attacks [10].

RECENT APPROACHES TO MIGRAINE THERAPY

The purpose of migraine therapy is to reduce the frequency of attacks and intensity of pain attacks to improve the patient's quality of life. Migraine therapy includes non-medical therapy as well as appropriate medical therapy including abortive therapy and prophylactic therapy. Non-medical therapy is to avoid triggering factors such as changes in sleep patterns, food and drink, monosodium glutamate, stress, bright light, flickering light, and high places. Abortive therapy is a therapy that can stop the progression of pain during an attack, including non-specific abortive therapy, namely non-steroidal anti-inflammatory drugs and symptomatic therapy, as well as specific abortive therapy such as triptans and ergot derivatives. Prophylactic therapy includes tricyclic antidepressants, serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, beta-blockers, calcium channel blockers, and antiepileptic drugs [11-13].

There are several prophylactic treatment options for migraine, but each therapy has some side effects such as weight gain or loss, hypotension, drowsiness, and fatigue. Migraine is often a progressive disorder and has an impact throughout the patient's life, thus diagnosis and selection of appropriate prophylactic therapy with the lowest side effects are very important in order to improve the quality of life of patients. Several supplementation therapies including magnesium, coenzyme Q10, B vitamins (B2, B3, B6, B9, and B12), melatonin, and omega 3 are thought to be effective as migraine prophylactic therapy [13]. Vitamin D is one of the supplementation agents thought to be associated with headaches and has a protective role in headache and migraine [14,15].

METABOLISM, PHYSIOLOGY AND BIOLOGICAL FUNCTION OF VITAMIN D

There are 2 forms of vitamin D, Vitamin D2 which is obtained from ultraviolet light irradiation on the mushroom sterol ergosterol, and Vitamin D3 which is synthesized from the cholesterol precursor 7-dehydrocholesterol in skin exposed to ultraviolet light and is found in oil-rich fish such as salmon, mackerel and herring. Vitamin D from skin and food is still in an inactive form and requires a hydroxylation process. The first hydroxylation occurs in the liver with vitamin D-25-hydroxylase to 25(OH)D. This 25(OH)D then undergoes hydroxylase in the kidney with enzyme 1α-OHase (CYP27B1) to active

form of vitamin D, 1,25-(OH)2 (calcitriol). Vitamin D hydroxylation pathway can be seen in **Figure 1**. Calcitriol binds to the nuclear vitamin D receptor (nVDR) which can be found in the kidney (which increases calcium reabsorption), small intestine (increases calcium and phosphate absorption), and other tissues. Calcitriol has variety of functions including suppression of cellular proliferation and stimulation of terminal differentiation, inhibition of angiogenesis, suppression of renin secretion, induces the production of cathelicidine by macrophages, and aids insulin secretion. Serum 25(OH)D concentration is used as a biomarker to assess vitamin D status in the body [16].

Recommended daily intake of vitamin D is differentiated by age as follows: 600 IU (15 mcg)/day for children aged 9-70 years and 800 IU (20 mcg)/day for adults over 70 years old. Vitamin D can be found in foods such as marine fish and fish oil, as well as egg and dairy products, but it is estimated that consumption from these foods will only meet about 20% of the recommended daily dose [9,16]. Lack of sun exposure, low daily consumption, impaired synthesis or vitamin D metabolism due to genetic factors, geographic factors, kidney disorders, endocrine disorders, parathyroidism, diabetes mellitus, and consumption of several drugs (anti-epileptic drugs, antiretrovirals, and azole antifungals) are risk factors for vitamin D deficiency [9].

Vitamin D is reported to play a role in several brain functions. Calcitriol can play a role in neuroplasticity, apoptosis and gene expression of neurotransmitter, neurotrophic and synaptic proteins related to central nervous system function [17]. In addition, vitamin D has also been reported to modulate levels of cellular oxidative stress, intracellular calcium concentrations, immune system function, and production of neuropathic factors as well as inhibition of the mechanisms of neurodegeneration at the cellular level [9].

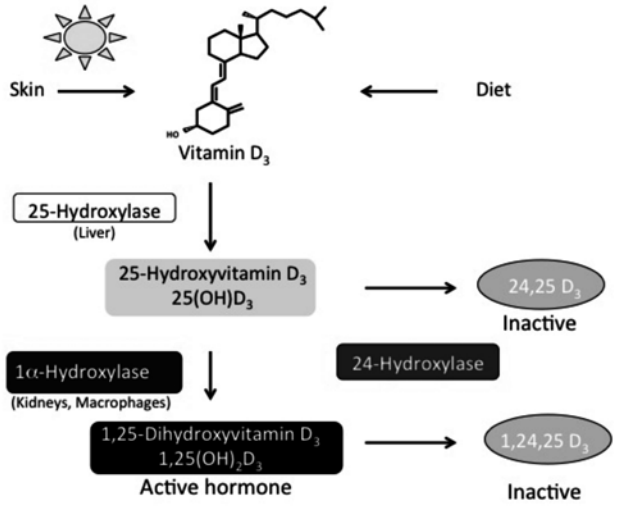

FIGURE 1. Hydrolysis Pathway of Vitamin D [18]

THE ROLE OF VITAMIN D IN HEADACHES AND MIGRAINES

Vitamin D deficiency is thought to be associated with various pain-related disorders, although there have been no reports of a causal relationship. Several clinical trials have reported vitamin D deficiency in patients with chronic pain, cancer-associated pain, and patients with persistent, unspecified musculoskeletal pain, and pain associated with rheumatological diseases. Pain was reported to be reduced after vitamin D supplementation, especially in samples that had an initial 25(OH)D serum level of less than 30 nmol/L, acts as a neuroactive steroid, inhibits its NO synthesis, and suppresses prostaglandins (PGE2) [19].

Vitamin D is thought to play a role in the mechanism of headache through several pathways. First, role of vitamin D in the regulation of the immune system and inflammation. Several studies reported that vitamin D supplementation increased secretion of anti-inflammatory factors such as IL-4, IL-5 and IL-10 and increased total antioxidant capacity [16]. In line with this, levels of proinflammatory agents such as C-Reactive Protein (CRP) , IFN-g, IL-1β, IL-6, TNF-α, IL-7 were also reported to be decreased [20].

Expression of nVDR on immune and inflammatory cells proves the role of vitamin D in regulating the activation, proliferation and differentiation of these cells [17]. Vitamin D contributes to suppression of inflammation by inhibiting cyclooxygenase-2 (COX-2) and inhibiting the production of prostaglandin E2 (PGE2). As an inhibitor of the adaptive immune system, vitamin D has been reported to suppress Th1 and Th17 proliferation and prevent the release of proinflammatory cytokines. This creates an imbalance between T helper cells with Th2 and regulatory T cells through an increase in IL-4 and the secretion of transforming growth factor-β (TGF-β) [17,20]. Dysregulation of Th1/Th2 balance is thought to contribute to migraine nociception [21]. Vitamin D is also associated with modulation of oxidative stress through regulation of the rate of oxygen consumption that is influenced by mitochondrial function [9].

Second, low serum 25(OH)D levels have been reported to be associated with high NO levels [22]. NO acts as a vasodilator factor that initiates migraine attacks through activation of the NO/cyclic guanosine monophosphate (cGMP) pathway in addition to increasing CGRP release, thereby stimulating nociceptive neurons in the trigeminovascular nervous system. In addition, NO can increase the production of substance P in perivascular nociception which

can increase inflammation in the central nervous system along with CGRP in the process of pain. These neurotransmitters may have an impact on nociceptive processes through their role in the formation of central sensitization in the posterior column of the spinal cord [9]. Those 1,25(OH)2D3 has been reported to control NO transcription in endothelial cells and thus modulate vascular function.

Another possible mechanism explaining the effect of vitamin D on migraine is the direct relationship between serum 25(OH)D concentrations and magnesium (Mg) levels [23]. In addition, Vitamin D may play a role in neuronal development and the biosynthesis of neurotransmitters and neurotrophic agents such as nerve growth factor (NGF), an important molecule that plays a role in the defense of hippocampal and neuronal cortical neurons. This vitamin is also associated with changes in levels of neurotransmitters such as glutamine, noradrenaline, dopamine, and serotonin [24].

Several studies reported vitamin D deficiency in migraine patients, while another revealed normal vitamin D levels (12.40-38.08 ng/ml) [25]. One case control study reported a higher serum vitamin D level, between 50-100 ng/mL, was associated with 80-83% lower odds of migraine headaches than those with serum levels below 20ng/mL. There were 19-22% decreased odds of developing migraine in every 5 ng/mL increase in serum 25(OH)D [26]. This founding also confirmed by Celikbilek et al that reveal serum vitamin D and VDR levels were lower in migraineurs than in controls, with no significant differences in VDBP levels between the groups [27].

VITAMIN D RECOMMENDATION ON MIGRAINE

Several studies have reported vitamin D therapy in patients with migraine. Mottaghi et al observed vitamin D supplementation of 50,000 IU/week for 10 weeks reporting a reduction in the number of headache attacks in patients with migraine. Although there was no reduction in CRP levels in these patients [28]. This was also evidenced by a study from Gazreani et al that evaluated the administration of vitamin D 4000 IU/day (100 mcg/day) versus placebo for 6 months in 48 migraine patients. He reported a significant improvement in the frequency of day attacks with headache in the intervention group. Although there was no difference in pain intensity in the two groups. There were no adverse effects of therapy in either group [29]. An interventional study observing migraine in children reported an improvement in the frequency of migraine attacks in the intervention group receiving amitriptyline therapy with complementary vitamin D therapy (400, 800, or 5000 IU/day) for 6 months. However, a randomized double-blind clinical trial by Knutsen et al reported no significant improvement in pain levels as measured by Visual Analog Score (VAS) and Headache Impact Test (HIT-6) in the group given vitamin D supplementation of 400 IU/day and 1000 IU/day compared to placebo [30].

Administration of low doses of vitamin D per day has been reported to be more effective than large doses of weekly or monthly. Vitamin D3 supplementation of 2000 IU/day can be used as maintenance therapy [31]. Administration of vitamin D3 supplementation up to 4000 IU in samples with normal serum 25(OH)D levels is still reported to be safe, thus vitamin D supplementation at a dose of 2000-4000 IU per day can be considered as complementary therapy to migraine. Particular attention should be paid to patients who are at risk of developing vitamin D hypovitaminosis such as obese patients, the elderly, people with insufficient sun exposure, patients taking glucocorticoid, anticonvulsant, antifungal and antiretroviral medications, patients with impaired absorption, hyperparathyroidism and patients with liver and kidney disorders [16].

CONCLUSION

Vitamin D is thought to contribute in reducing headache attacks in patients with migraines. Considering that there are quite number of studies reporting vitamin D deficiency in patients with migraine, vitamin D supplementation may be considered as a complementary therapy. There is still a need for both prospective large sample cohorts and large randomized control studies to assess the relationship between pain characteristics including frequency, intensity and duration with serum 25(OH)D in patients with migraine and the effect of vitamin D therapy on migraine.

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