



The role of nutrients in the pathogenesis and treatment of migraine headaches: Review



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ABSTRACT

Objective: Migraine as a disabling neurovascular disease affects 6% of men and 18% of women worldwide. The deficiency of many nutrients including magnesium, niacin, riboflavin, cobalamin, coenzymes Q10, carnitine, α -lipoic acid and vitamin D is associated with migraine. Some researchers postulate that mitochondrial dysfunction and impaired antioxidant status can cause migraine. Also increase in homocysteine level can lead to migraine attacks; therefore, some Nutraceuticals play a vital role in migraine prevention. Thus, the aim of the current study was to review randomized controlled trials (RCT) assessing the effect of nutritional supplements on migraine patients.

Methods: English articles in the following databases were searched: MEDLINE, AMED, EMBASE and Cochrane Library. In this manuscript, RCTs published during 1990–2017 were reviewed.

Results: Evidences indicate that supplementation with magnesium, carnitine, riboflavin, niacin, CoQ10, vitamin D, Vitamin B₁₂ and alpha lipoic acid have prophylactic and therapeutic effects on migraine patients.

Conclusion: Due to the possible side effects of pharmacological drugs and drug addictions, the use of nutrient compounds alone or in combination with routine cures have been proposed. However, further constructive studies are required.

1. Introduction

Migraine is a primary headache disorder diagnosed by recurrent and moderate to severe headaches. These unilateral and pulsating headaches last from 4 to 72 hours [1]. Associated symptoms include nausea, vomiting, sensitivity to light, sound and odor. Physical activity may increase the intensity of pain [2]. Migraine attacks may be with or without aura (a short period of visual disturbance signaling headache occurrence). Occasionally, an aura sometimes occurs with headaches [3]. Migraine is the second main cause of headaches after tension type headaches. Migraine is a debilitating brain disorder with serious social and financial consequences for the individual and the society [4]. The incidence of migraine is higher among women due to hormonal influences [5]. Although the main cause of migraine is unknown, various factors such as genetics and environmental factors, are involved in the onset of migraine attacks [6]. Mutation in the MTHFR gene, abnormal level of vitamin D, production of inflammatory agents around the nerves and cerebrospinal fluid, low serotonin level, increased calcitonin

gene related peptide (CGRP), matrix metalloproteinase 9 (MMP-9), homocysteine and nitric oxide (NO) levels, mitochondrial dysfunction and decreased level of metabolic enzymes are among the most important causes of migraine [7–11]. In migraine-susceptible people, vasoactive peptides such as CGRP and substance P, are released from trigeminovascular neurons. These peptides exacerbate vasodilation and cause neurogenic inflammation which may lead to vasodilation and leakage of blood vessels [12]. Vasodilation and neurogenic inflammation increase activation of trigeminovascular neurons and modulate transmission of pain impulses in the brain. Studies have indicated that inflammatory factors, such as tumor necrosis factor- α (TNF- α), increase CGRP transcription [13].

Migraine drug treatments aim to prevent headache attack or reduce the intensity and frequency of attacks, particularly when they are characterized by intense pain. Triptans can be considered as important drugs for acute treatment; they effect serotonin (5-HT) 1B/D/F receptors located on presynaptic trigeminal nerve endings of vascular smooth muscle and the central nervous system (CNS) [14–16]. In

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Table 1
Summary of clinical trials regarding Magnesium in migraine treatment.

Author	Design	Medication and subjects (n)	Dose	Results	Ref.
Peikert et al. (1996)	RCT	81 migraine patients	600 mg/day	Magnesium reduced frequent migraine attacks in patients.	[45]
Demirkaya et al. (2001)	RCT	120 migraine patients With acute attack	1gr/day IV	Magnesium reduced the symptoms of migraine	[46]
Wang et al. (2003)	RCT	118 children with migraine headache	9 mg/kg per day	They observed oral magnesium oxide is not superior to placebo in preventing frequent migrainous headache in children	[47]
Bigal et al. (2002)	RCT	180 migraine patients	1gr/day IV	Magnesium intake improved pain and symptoms in patients	[48]
Rahimdel et al. (2007)	RCT	120 migraine patients	1gr/day IV	After 60 minutes of receiving magnesium the severity of migraine headaches decreased significantly	[49]
Köseoglu et al. (2008)	RCT	40 patients with Migraine without aura	600 mg/day	Magnesium significantly reduced the severity and frequency of migraine attacks	[50]
Tarighat et al. (2012)	RCT	33 migraine patients	500 mg/day	Magnesium supplementation reduced the severity and frequency of migraine attacks	[22]
Tarighat et al. (2012)	RCT	35 migraine patients	500 mg/day	Concurrent Mg–L-carnitine supplementation significantly reduced migraine frequency and severity	[22]

addition to tryptan, various other drugs including beta blockers, tricyclic antidepressants, calcium channel blockers, NSAIDs, and anticonvulsants are used in treating migraine [16,17].

In addition to preventive treatments, some minerals such as (Mg), coenzymes Q10 (CoQ10), a-lipoic), vitamins (B₂, B₃, B₁₂, D) and carnitine, are often considered as nutrients rather than drugs and are effective in migraine prevention [18–22].

Researchers have measured the baseline levels of riboflavin, vitamin D, folate, CoQ10 and magnesium in migraine patients. A high percentage of patients have CoQ10, vitamin D, riboflavin, magnesium deficiencies. Interestingly, young women and girls are more likely to experience CoQ10 deficiency and boys are susceptible to vitamin D deficiency. Additionally, an association between migraine and cardiovascular diseases and mortality is mentioned among women. Patients suffering from chronic migraines at regular intervals are in risk of CoQ10, magnesium, vitamin D and riboflavin deficiency, compared to those with episodic migraines with infrequent intervals. Since there is no comprehensive study reviewing the effects of dietary supplements on migraine patients, the purpose of this review was to determine the effect of mineral, coenzyme and vitamin deficiencies in the pathogenesis of migraine headaches and their potential therapeutic effect on migraine.

2. Magnesium

Magnesium is the second frequent intracellular cation present in all tissues. Magnesium plays many roles in the human body. It contributes to intracellular energy storage and expenditure, acts as a cofactor in many enzymes, is required for nucleic acid synthesis and is involved in cell division and growth, as well as regulation of ion channels, receptors and the transport system. Migraine is likely considered as a brain excitability disorder [23]. Magnesium deficiency may increase the sensitivity of migraine neuro-inflammation, calcium channel and N-methyl-D-aspartate (NMDA) receptor blockade, glutamate and nitric oxide activity, serotonin receptor affinity, and endogenous hormone regulation [24]. Magnesium has an important role in the regulation of NMDA glutamate receptors which are involved in pain transmission inside the nervous system and controlling brain blood flow [25,26]. Magnesium blocks NMDA receptors and prevents the entry of calcium into cells [27,28]. As such, low magnesium level accelerates activation of NMDA receptors which provoke the entry of calcium into cells and effects neurons and cerebral vascular muscles. Therefore, magnesium acts as an NMDA receptor antagonist. Studies have shown that NMDA receptors play an important role in the onset and progression of Cortical Spreading Depression (CSD) [29,30]. The CSD theory is related to the

extension of migraine aura [31–33]. One of the important mechanisms that has been considered to increase the sensitivity of the brain to this phenomenon is alteration of mitochondrial metabolism. Magnesium deficit may lead to CSD through alteration of oxidative phosphorylation and neuronal polarization in the mitochondria [34]. Therefore, by counteracting vasospasm, inhibiting platelet accumulation, stabilizing cell membranes and decreasing the formation of inflammatory mediators, magnesium may beneficially target different aspects of the neurogenic inflammation which occur during migraine and eventually improve mitochondrial oxidative phosphorylation, 5-HT neurotransmission and the NO system [35]. One of the primary scientific studies by Nuclear magnetic resonance spectroscopy reported the role of magnesium in migraine and magnesium level decrease in patients when compared to healthy controls [36]. Also, several studies have shown that serum level of magnesium in migraine patients is lower than healthy subjects [37–43]. Intravenous (IV) magnesium administration is routinely offered for acute migraine, as well as prophylaxis, while oral magnesium supplementation is prescribed for prophylaxis. The American Academy of Neurology (AAN) has revealed the effectiveness of oral magnesium usage in migraine prevention (level B evidence). A meta-analysis [44] assessing the effectiveness of IV magnesium in acute migraine treatment suggested level of U for IV magnesium. The suggested dose of magnesium supplement is 400 mg per day, and can be raised up to 1200 mg, if tolerated. Possible gastrointestinal adverse effects of magnesium supplementation are abdominal pain, nausea and diarrhea [35]. Among the various forms of magnesium supplements, magnesium glycinate and other amino acid-chelated forms are likely to be tolerated [35]. Table 1 demonstrates the effects of magnesium on migraine symptoms in various clinical trials.

3. Riboflavin

Riboflavin plays an important role in the metabolism of carbohydrates, fats, and proteins. Riboflavin, or vitamin B₂, is considered as an essential component and precursor of riboflavin 5'-phosphate, known as Flavin mononucleotide (FMN) and Flavin adenine dinucleotide (FAD) [51]. This vitamin participates in the electron transport chain (ETC) and is required for the activity of flavoenzymes. Several factors may contribute to the pathogenesis of migraine, such as mitochondrial dysfunction resulting in oxygen metabolism insufficiency and changes in mitochondrial energy metabolism [52]. As a result, decrease in mitochondrial phosphorylation potential in between attacks has been observed among patients with migraine. Many studies have reported that vitamin B₂ in high doses could be effective in migraine prophylaxis. Patients may not have enough Vitamin B₂, so this vitamin could

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