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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 B_{12} 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 (B_2, B_3, B_{12}, 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 B_2, 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 B_2 in high doses could be effective in migraine prophylaxis. Patients may not have enough Vitamin B2, so this vitamin could

Table 2
Summary of clinical trials regarding Riboflavin for migraine treatment.

Author	Design	Medication and subjects (n)	Dose	Results	Ref
Schoenen (1994)	Pilot study	49 patients with migraine	400 mg/day	Riboflavin supplementation improved symptoms of migraine	[55]
Schoenen (1998)	RCT	55 patients with migraine	400 mg/day	Riboflavin significantly reduced the frequency of migraine attacks	[56]
Sandor (2000)	RCT	26 patients with migraine	400 mg/day	Riboflavin reduced the symptoms of migraine	[57]
Boehnke (2004)	RCT	23 patients with migraine	400 mg/day	Riboflavin reduced the frequency of migraine attacks	[58]
Maizels (2004)	RCT	49 patients with migraine	400 mg/day	Riboflavin 25 mg showed an effect comparable to a combination of riboflavin 400 mg, magnesium 300 mg, and feverfew 100 mg	[59]
MacLennan (2008)	RCT	48 children with migraine	200 mg/day	Riboflavin had no significant effect on migraine symptoms	[60]
Condò(2009)	Retrospectie	41 pediatric and adolescents with migraine	200 mg/day	Riboflavin significantly reduced migraine frequency	[61]
Bruijn (2010)	RCT	42 children with migraine and tension headaches	50 mg/day	No significant difference in mean frequency of migraine attacks was observed	[62]
Rahimdel et al. (2015)	RCT	90 migraine patients	400 mg/day	vitamin B2 supplementation reduced migraine attacks	[63]

RCT: Randomized Clinical Trial.

Table 3
Summary of clinical trials using CoQ10 for treating migraine.

Author	Design	Medication and subjects (n)	Dose	Results	Ref.
Rozen et al. (2002)	RCT	32 Patients with a history of episodic migraine	150 mg/day	CoQ10 significantly reduced frequency of migraine attacks.	[64]
Sandor et al. (2005)	RCT	42 migraine Patients	300 mg/day	CoQ10 significantly reduced frequency of migraine attacks, headache-days and days-with-nausea	[76]
Hershey et al. (2007)	RCT	252 migraine patients with low CoQ10 levels	1 to 3 mg/kg per day	serum level of CoQ10 increased with a significant reduction in headache frequency	[77]
Slater et al. (2011)	RCT	120 children and adolescents with migraine headache	100 mg/ day	CoQ10 significantly reduced the severity and frequency of migraine attacks	[78]
Shoeibi et al. (2017)	RCT	80 patients with migraine headache	100 mg/ day	CoQ10 significantly reduced the severity and frequency of migraine attacks	[79]
Dahri et al. (2017)	RCT	Eighty-four women with episodic migraine	400 mg/day	CoQ10 supplementation significantly reduced the frequency, severity and duration of migraine attacks	[80]

be a potential treatment for migraine. Even though evidences obtained from clinical trials aren't strong, both the AAN (level B evidence) [53] and the Canadian Headache Society recommend its consumption in adults with migraine, because it is well tolerated and side effects are limited and mild [54]. The recommended dose of riboflavin in adult migraineurs is about 400 mg per day. Based on studies, riboflavin has not been shown useful in migraine prevention in children and therefore is not recommended. Table 2 summarizes clinical trials regarding Riboflavin for treating migraine.

4. Coenzyme Q10

Coenzyme Q10 is a naturally hydrophobic substance and is an essential element of the mitochondrial electron transport chain [64]. CoQ10 is a substance that is both synthesized in the body and absorbed from food sources; however, its total absorption is inadequate for pathological conditions [65]. CoQ10 has many roles in the body, including: transferring electrons throughout the inner mitochondrial membrane from the NADH dehydrogenase complex (complex I) and the Succinate-Q-reductase complex (complex II) to cytochrome C [66], acting as an antioxidant and helping protect the myocardium from post-ischemic renewed damages. Elevated level of MMP-9 is associated with blood-brain barrier (BBB) dysfunction and inflammation of nerves exacerbate migraine attacks [67]. In addition, animal studies have shown that BBB dysfunction and other MMP-9-related mechanisms develop the onset of CSD which is the main mechanism of migraine attacks [68]. Imamura et al showed that MMP-9 level is higher in migraine patients than healthy subjects [69]. Active oxygen species, especially H_2O_2, are one of the most important factors in the expression and regulation of Matrix metalloproteinase. In addition, Tumor Necrotizing Factor-α and Interlukine-6 regulate the expression of MMPs [70]. CoQ10 is one of the most important antioxidants that acts against H_2O_2 and reduces the expression of cytokines and MMPs [65]. CoQ10 also improves exercise tolerance, muscle weakness, reduces serum pyruvate and lactate levels, and accelerates post-exercise recovery of phosphocreatine in patients with mitochondrial encephalomyopathies [71,72]. In the United States, CoQ10 is known as an over-the-counter (OTC) dietary supplement. In patients with mitochondrial dysfunction, under certain conditions, CoQ10 is associated with increased oxidative stress and acts as a useful therapeutic agent. Several studies have shown that serum lactate and pyruvate level are higher in migraine patients than healthy subjects [73]. On the other hand, CoQ10 supplementation improves muscle and brain energy metabolism in patients with mitochondrial cytopathies [74]. The AAN considers CoQ10 useful in migraine prevention (grade C quality evidence) [53], and the Canadian Headache Society guidelines strongly recommend CoQ10 as a migraine preventative agent [54]. Although the effective dose of CoQ10 is unclear, 1–3 mg/kg per day is recommended [75]. Table 3 summarizes RCTs using CoQ10 as a therapeutic nutrient for treating migraine.

5. Vitamin D

Vitamin D is a fat-soluble vitamin present in slight amounts in food. It is usually added to food and is available as a supplement. When the skin is exposed to sunlight, vitamin D is produced in the body. Vitamin D plays important roles in the body such as increasing calcium

absorption, developing healthy bones, protecting older people from osteoporosis, immune system reinforcement and decreasing inflammation. A number of case studies have reported the positive effects of vitamin D supplementation in headache and migraine [81,82]. A case study performed on two groups of women with migraine associated with menstruation and premenstrual syndrome indicated that patients had inadequate vitamin D levels. After two months of treatment, it was observed that vitamin D and calcium supplementation (1600-1200 IU per day) significantly decreased migraine attacks and premenstrual symptoms [83,84]. In another study on postmenopausal patients with migraine and low level of vitamin D, vitamin D and calcium supplementation reduced the frequency and duration of migraine attacks. In a study on eight patients with chronic tension-type headache, vitamin D deficiency, and osteomalacia, demonstrated that daily intake of vitamin D and calcium supplementation (1500 IU vitamin D3 and 1000 mg calcium) improved symptoms of headaches during 4–6 weeks, while after one week of treatment, serum level of calcium became normal. The exact relationship between vitamin D deficiency and headache is unclear. The most important mechanisms involved in headache include possible sensitization of second and third neurons due to continuous stimulation of sensory receptors of periosteal covering and central sensitization. Low serum level of magnesium is another possible mechanism associated with vitamin D deficiency [85]. A possible mechanism for the pathogenesis of tension-type headache is the abnormal metabolism of magnesium. Since the intestinal absorption of magnesium is dependent on vitamin D [85], thus reduction of magnesium absorption due to vitamin D deficit may lead to tension-type headache. Another mechanism associated with tension-type headache is the presence of vitamin D receptors, 1-hydroxylase (the enzyme responsible for the formation of the vitamin D active form), vitamin D binding protein in the brain and particularly hypothalamus [11]. Table 4 summarizes studies investigating the effects of vitamin D in people with headache.

6. Vitamin B_3

Niacin, is an organic compound known as nicotinic acid, and is an essential nutrient. Niacin and nicotinamide are two of the various forms of the vitamin B3 complex. Limitation of scientific information has caused complexity in the relationship between niacin and migraine. Niacin is a vitamin that plays an important role in dilatation and widening of blood vessels. Because migraine headaches are related to the contraction of blood vessels in the brain, Niacin is not generally considered to be effective for migraine prevention. However, low plasma level of serotonin has been involved in the pathogenesis of migraine. Niacin may act as a negative feedback regulator in the kynurenine pathway to shunt tryptophan into the serotonin pathway, which eventually leads to higher plasma serotonin level [90]. Niacin has been studied as a potential treatment for migraine. In contrast, few studies have reported side effects for niacin in cases of headaches, particularly migraine. Additionally, headaches, but not specifically migraine headaches, have been reported as infrequent side effects of niacin consumption. The effectiveness of niacin in treating headaches requires further randomized controlled trials. In acute migraine headaches, activation of the trigeminovascular complex causes several symptoms. On the other hand, this complex leads to intracranial vasoconstriction followed by, migraine aura and headache due to vasodilation of the extra cranial vessels and activation of the perivascular nociceptive nerves. Intravenous and oral administration of niacin, may prevent the symptoms of migraine by dilating the intracranial vessels and subsequent contractions of the extracranial vessels. According to results, niacin could be considered as a peripheral vasodilator, however, its impact on the main central mechanisms involved in migraine headaches (cerebral blood) has not been completely investigated. By inducing the production of prostaglandin D_2 (PGD_2) in the skin, Niacin causes lateral dilation and cutaneous blushing which leads to an increase in the levels of PGD_2, 9α, 11β-PGF_2 and other metabolites in the plasma [91]. Administration of niacin at doses of 500 mg orally or topically in the form of methyl nicotinate significantly increases the release of prostaglandin D_2 in the skin and its metabolites in the plasma [91,92]. It is not entirely clear whether prostaglandin D_2 affects the intracranial arteries, however, since niacin aborts acute migraine attacks, it seems applicable. Bicknell and Prescott [92], demonstrated that niacin has an important role in the vasodilation of the cerebral and spinal vessels, so intravenous injection increases the rate of intracranial blood flow without any alteration in blood pressure. Unfortunately, there is not enough evidence for the effect of niacin on increasing the rate of blood flow. From the perspective of tension-type headaches, intravenous niacin is beneficial due to its central vasodilator properties. Central mechanisms such as the trigeminal system are responsible for the underlying pathophysiology of chronic tension-type and migraine headaches [93]. There is also cerebrospinal or intracranial venous pressure in chronic tension-type headaches [93]. Although chronic tension-type migraine headaches are not the same, they are very similar, which can be due to the escalating pathophysiological procedures [94]. Therefore, based on the same hypothesized mechanism of action described previously, niacin may be helpful in relieving the acute phase of tension headaches. A number of studies have reported prophylactic beneficial effects for niacin when administered orally. Recently, it has been proved that mitochondrial energy metabolism disorders play an important role in triggering migraine headaches [95]. Niacin may be a useful migraine preventive agent due to increasing substrate availability to complex I, maintaining sufficient mitochondrial

Table 4
Summary of studies examining the relationship between vitamin D and migraine attacks.

Author	Type of study	Exposure variable	Exit variable	Result	Ref.
Thys-Jacobs (1994)	Case -Report	Vitamin D and calcium	Migraine associated with menstruation	A significant reduction in migraine attacks during two-months treatment with calcium and vitamin D	[83]
Thys-Jacobs (1994)	Case- Report	Vitamin D and calcium	Migraine	The frequency and duration of migraine headaches during calcium and vitamin D intake was reduced	[84]
Mitsikostas et al. (1996)	cross-sectional	latitude	Headache frequency	Higher prevalence and frequency of headache was reported in the northern regions compared to the southern regions	[86]
Turner et al. (2008)	Retrospective	Prevalence of vitamin D deficiency	People with chronic pain	The prevalence of vitamin D deficiency was about % 26	[87]
Prakash et al. (2009)	Case -Report	Vitamin D and calcium	headache	Daily intake of vitamin D and calcium for 4-6 weeks improved headache	[85]
Knutsen et al. (2010)	cross-sectional	Vitamin D	headache	Inverse relationship between headache and vitamin D was reported	[88]
Kjaergaard et al. (2012)	cross-sectional	Vitamin D	headache	No correlation between serum level of vitamin D and migraine was mentioned	[89]

Table 5
Summary of studies investigated Niacin's Effectiveness for the Treatment migraine.

Author	Condition	N	Design	Study	Results	Ref.
Atkinson et al (1944)	Migraine headaches	21	One initial intramuscular injection (IM) followed by a series of 6 or 8 intravenous (IV) treatments (maximum 50 mg), then regular IM injections (25–50 mg) combined with 50–150 mg of oral administration.	case-series	17 patients had positive response.	[99]
Goldzieh et al. al (1946)	Headaches of different etiologic types	100	100 mg of IV sodium nicotinate or niacin	case-series	75 patients had complete relief.	[100]
Grenfell et al. (1949)	Migraine headaches	15	100 mg of IV niacin, and an additional 50–200 mg if necessary to ensure a flushing response of more than 15- minutes.	case-series	13 patients had positive response. Headaches were relieved in 27 of the 31 times	[101]
Grenfell et al. (1951)	Tension headaches	35	22 subjects received 100–200 mg of IV niacin for a total of 53 times.	case-series	13 of the 22 subjects had a positive response. The headaches were relieved in 41 of the 53 times when niacin was administered by IV administration.	[102]
Morgan et al. (1953)	Tension headaches	5	100 mg of IV niacin regularly for 12 weeks combined with a graded schedule of oral dosing, beginning at 300 mg daily, increasing to 900 mg daily, and tapering down to 300 mg daily.	case-series	All 5 cases of emotional or tension headaches were very responsive to both IV and oral niacin.	[103]
Morgan et al. (1955)	Tension headaches	50	100 mg of IV niacin regularly for 23 weeks and then continued once every 2 months and as needed. This was combined with a graded schedule of oral dosing, beginning at 300 mg daily, increasing to 900 mg daily, and tapering down to 300 mg daily.	case-series	In 44 of the 50 subjects the results of niacin therapy was satisfactory.	[104]
Hall et al. (1991)	Migraine headaches	1	300–500 mg of niacin were chewed	case-report	Resolution of migraine headaches	[105]
Prousky et al. (2003)	Migraine headaches	2	500 mg of oral niacin taken at the onset of acute symptoms.	case-report	In 2 of the 2 subjects, niacin aborted the acute migraine symptoms. In the first subject, niacin resolved the acute attacks in 4 of 4 occasions. In the other subject, niacin resolved the attack on one occasion.	[106]
Velling et al. (2003)	Migraine headaches	1	375 mg of oral sustained-release niacin twice daily for 1 month, and 375 mg once daily for 2 months.	case-report	Migraine-free for the first month, and a marked reduction in migraine headaches over the next 2 months.	[90]

energy metabolism [96]. In addition, riboflavin and COQ10 are also responsible for the complex I reinforcement of the mitochondrial respiratory chain [55,56,64]. Niacin improves mitochondrial energy metabolism and increasing blood flow and oxygenation to the skeletal muscles and prevents tension-type headaches. The overall effect of reducing episodes of muscular tension and soreness could be related to the reduction of lactic acid concentration. Niacin improves the mitochondrial energy metabolism by reducing the concentration of lactic acid. On the other hand, studies have shown that niacin supplementation decreases blood lactate and pyruvate concentration in over 50% of patients with mitochondrial encephalopathy, myopathy, lactic acidosis, and stroke-like episodes [97]. This mechanism may be accurate in patients with migraine, since plasma level of lactate and pyruvate are higher in patients with migraine than patients with tension-type headaches or normal subjects [98]. Table 5 summarizes studies investigating the effects of niacin in people with headache.

7. Vitamine B_{12}

Vitamin B12, also called cobalamin, is one of the members of the vitamin B family. Methyl cobalamin and adenosyl cobalamin are the active forms of vitamin B12 in mammals. Besides the two forms mentioned, circulating vitamin B12 is also present as hydroxycobalamin. Vitamin B12 is involved in several pathways. Studies have demonstrated that Hydroxycobalamin has scavenging action against NO [107]. Nitric oxide is involved in pain transmission, hyperalgesia, chronic pain, inflammation, central sensitization and mostly the cyclic guanosine mono phosphate (cGMP) dependent pathway [9,108]. Based on this hypothesis, vitamin B12 acts as a scavenger against NO, thus it plays an important role in migraine prophylaxis [109]. In an open trial assessing the effect of hydroxycobalamin in prevention migraine, intranasal administration of hydroxocobalamin decreased the frequency of attacks by about 50% in 53% of migraine patients [110]. As mentioned earlier, other vitamins, such as riboflavin, niacin and coenzymes, such as coenzyme Q10, have been suggested for their role in migraine prevention, based on the hypothesis that they improve mitochondrial production of adenosine triphosphate (ATP). Thus, we can understand a common mechanism between these compounds and vitamin B12. In fact, elevated NO level is able to inhibit the respiratory chain by binding to complex I and III and cytochrome C oxidase [111,112]. Similar effects have been mentioned for NO donors, which determine the production of proxy nitrite, a toxic subcellular components present in the mitochondria [113]. It has also been noted that the mitochondria is able to produce NO radicals [114]. Riboflavin is one of the components involved in the synthesis of B12 [115], both of these vitamins have revealed anti-nociceptive and anti-inflammatory effects in animal models [116].

Evidences indicate an association between gastric damage and migraine. Gastric mucus damage, observed in migraine patients, could be due to excessive consumption of NSAIDs, which are used in migraine attacks. Excessive use of NSAIDs causes gastrointestinal distress, reduces gastric mucus production along with bleeding, and causes gastric ulceration [117]. Gastric damage could also cause intrinsic factor deficiency and thus decrease vitamin B12 absorption and finally affect the important metabolic functions regulated by vitamin B12. When 225 migraine patients were evaluated for Helicobacter pylori, 40% of results were positive. After eradicating H. pylori, the intensity, duration, and frequency of migraine attacks were significantly reduced [118,119].

Several studies have mentioned an association between vitamin B12 pathway dysfunction and headache pathogenesis. Low serum levels of vitamin B12, folate and B6 are correlated with high levels of homocysteinemia, and plasma homocysteine level may be reduced by folic acid supplementation [120]. Vitamin B12 and folate are involved in the remethylation and synthesis of S-adenosylmethionine (SAMe). [121] Vitamin B12 and folate serum level reduction are observed in a majority of patients suffering from migraine [122]. Moreover, basal level of homocysteinemia, is considered to be a reliable marker of vitamin B12 deficiency which is higher among these patients, especially in migraineurs with aura. After compensating deficiencies, migraine index values are significantly reduced in respect to basal level. Until now the possible correlation between migraine severity and blood homocysteine level and the possible role of hyperhomocysteinemia as a causative factor in the predisposition of migraine has not been fully investigated [123]. Increased level of homocysteine in the brain may act as a trigger or amplifier via various putative mechanisms. Homocysteine acts as an antagonist to gamma-amino butyric acid (GABA)-A receptor [124], whereas few anti-migraine preventive drugs such as amitriptyline are strong GABAergic agonists [124], thus homocysteine may negatively modulate pain threshold in migraine patients. Since treatment with (NMDA) receptor antagonists is effective in inhibiting CSD [125], whereas homocysteine is a potent excitatory neurotransmitter that acts via activating NMDA receptor [126]. It is mentioned that elevated homocysteine level in the brain may augment negative electrophysiological hyperactivity. In addition, homocysteine has inflammatory properties. The final potential connection between brain homocysteine and migraine is oxidative stress. Homocysteine could increase oxidative stress by inhibiting the function of key antioxidant enzymes, such as extracellular superoxide dismutase [127], which in turn is associated with migraine [128]. Further studies are essential to substantiate putative mechanisms (Fig1).

8. Alpha lipoic acid

Alpha-lipoic acid **(ALA)** is a nutritional coenzyme involved in the energy metabolism of proteins, carbohydrates and fats, which has physiological functions in blood glucose disposal, and is able to scavenge a number of free radicals [129]. ALA is normally synthesized in animal origins and is essential for aerobic metabolism. It is also manufactured and available as a dietary supplement with antioxidant and pharmaceutical properties. Similar to riboflavin, niacin and COQ10, alpha lipoic acid enhances mitochondrial oxygen metabolism and ATP production [130]. In a small double-blind trial, supplementation with 600 mg of ALA once a day for three months significantly reduced the frequency of migraine attacks. However, this improvement was not statistically significant when compared to the changes observed in the placebo group. Additional research is needed to determine the effectiveness of ALA in preventing migraines.

9. L-carnitine

Carnitine (4-N-trimethylammonium-3-hydroxybutyric acid) plays a critical role in energy production, transportation of long-chain fatty acids across the inner mitochondrial membrane for β-oxidation and ATP production [131]. L-carnitine deficiency changes the oxidation of fatty acids and increases toxins that are originated from nociceptive triggers [132]. In fact, carnitine deficiency decreases beta-oxidation. Migraines and migraine triggers are associated with oxidative stress [133]. As mentioned earlier, antioxidants help give an end to oxidative stress and migraines [134]. L-carnitine, as a cofactor, has an important role in the transportation of free fatty acids (FFA) from the cytosol to the mitochondria. Free fatty acids degrade to Acyl-CoA by h-oxidation and enter the tricarboxylic acid (TCA) cycle. A large amount of oxygen is consumed in this reaction and ATP is synthesized in ETC and oxidative phosphorylation. Oxygen is reduced to H_2O at the end of the TCA cycle and decreases oxygen concentration leading to reduced ROS formation [135].

L-carnitine prevents oxidative damage and regulates nitric oxide, cellular respiration and the activity of enzymes involved in defending against oxidative damage [131]. Additionally, L-carnitine has a protective effect on the activity of mitochondrial enzyme succinate dehydrogenase as well as antioxidant enzymes, catalase and superoxide dismutase against 3-NPA-induced neurotoxicity [131]. Although

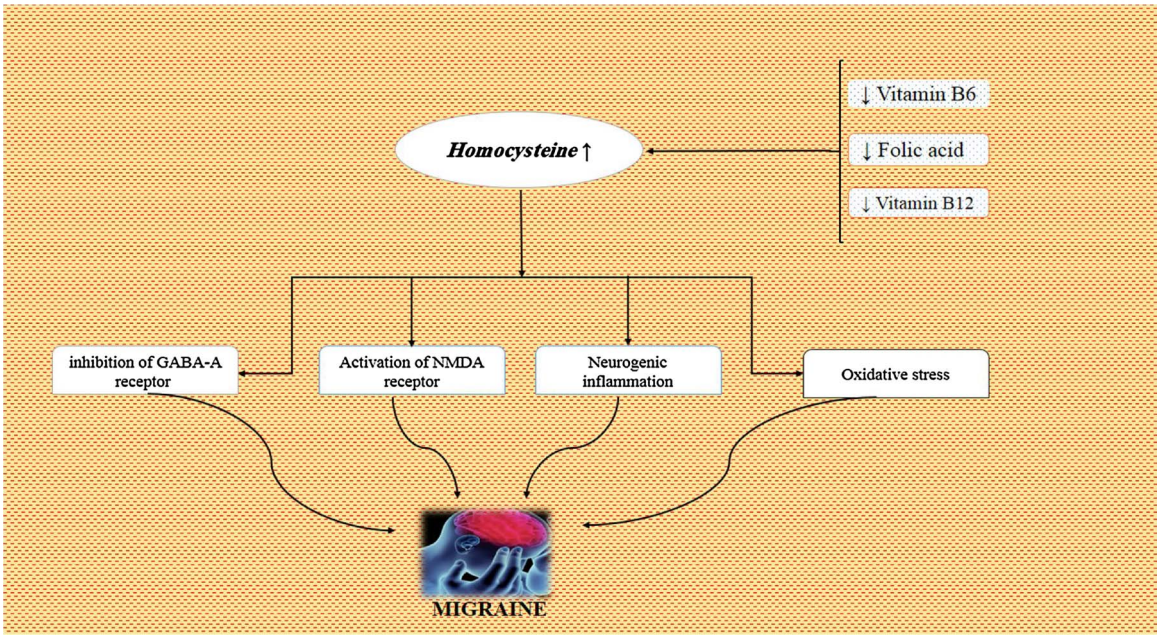

Fig. 1. Pathophysiological connection between elevated generation of homocysteine in the brain and migraine.

carnitine deficiency has not been considered as a factor in increasing the number of migraine attacks, it has been associated with low level of carnitine in patients with renal failure on dialysis. Carnitine supplementation improves headache pains [136]. Another explanation for the association between migraine and carnitine deficiency is improvement of carnitine level via riboflavin replacement [137]. Few studies have examined the effect of carnitine on migraine patients. Tarighat et al evaluated the effects of magnesium, L-carnitine, and concurrent magnesium–L-carnitine supplementation in migraine prophylaxis. In this single-blind clinical trial, subjects were assigned into four groups: 500 mg/day magnesium oxide (n = 33), 500mg/day L-carnitine (n = 35), 500 mg/day magnesium oxide and 500 mg/day L-carnitine concurrently (n = 30), or the control group (n = 35). According to their results, L-carnitine supplementation significantly decreased migraine frequency, severity, index and migraine days [22]. In another study, Kabbouche et al reported that L-carnitine supplementation reduced migraine frequency and severity [132]. Despite, the number of studies indicating positive results for L-carnitine supplementation in migraines, in a triple-blind crossover study, Hagen et al showed no significant differences in headache outcomes between acetyl-carnitine and placebo [138].

10. Conclusion

Nowadays complementary and alternative medicines are widely used. Considering the complex pathogenesis of migraine, various drugs have been used for its treatment. However, these drugs have possible side effects. In patients who suffer from these side effects and are not treated efficiently by prophylactic drugs, considering a nutraceutical agent for migraine prevention might be a wise choice. New approaches for improving headache symptoms in migraine patients include using nutrient compounds such as Magnesium, CoQ10, ALA, L-carnitine and vitamins (B_2, B_3, B_{12} and D), all of which have minimal adverse effects. These nutrients reduce the frequency and severity of migraine attacks via positive effects on mitochondrial function, reducing inflammatory factors and improving antioxidant status. Using effective nutrients along with prescribed drugs leads to decreased dosage of drugs required for the treatment of headaches and may reduce the side effects drugs.

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