Effectiveness of Riboflavin on Migraine

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Riboflavin (vitamin B2) is an essential water-soluble vitamin that helps prevent various medical conditions, such as sepsis, ischemia, and some cancers. Riboflavin's biological effects, including antioxidant, anti-aging, anti-inflammatory, and anti-nociceptive effects, have been extensively studied. The pathophysiology of migraines is linked to oxidative stress with mitochondrial dysfunction, and neuroinflammation by the glial cell network.

migraine riboflavin mitochondria inflammation oxidative stress

1. Introduction

Riboflavin (vitamin B2) is an essential water-soluble vitamin that helps prevent various medical conditions, such as sepsis, ischemia, and some cancers [1]. Riboflavin's biological effects, including antioxidant, anti-aging, anti-inflammatory, and anti-nociceptive effects, have been extensively studied. The pathophysiology of migraines is linked to oxidative stress with mitochondrial dysfunction [2][3][4], and neuroinflammation by the glial cell network [5]. Riboflavin might help improve migraines through various mechanisms, including oxidative stress and neuroinflammation reduction [6].

Riboflavin is heat stable, and cooking does not lower riboflavin levels; however, exposure to light can destroy it. Riboflavin is found in a variety of food sources. Milk products are a rich source, and green vegetables, such as broccoli, collard greens, and turnips, are moderate sources of riboflavin. Surprisingly, 10–15% of the world's population is genetically restricted in riboflavin absorption and utilization, and there is a potential for biochemical riboflavin deficiency worldwide [7]. Riboflavin deficiency across European countries ranges from 7–20% [8]. Metabolic triggers of migraines, such as fasting and skipping meals, directly link with energy homeostasis and may be associated with riboflavin deficiency. However, there is no evidence that riboflavin deficiency causes or aggravates migraine headaches.

Why is riboflavin administered to migraineurs i.e., patients with migraines? Patients with mitochondrial encephalomyopathy suffer from migraine-like headaches that are relieved by riboflavin; thus, prophylactic riboflavin administration has been attempted [9]. Riboflavin prophylaxis is recommended in adult guidelines [10][11] and has been shown to be somewhat effective in children [12][13]. A migraine is a common yet highly disruptive disease [14]. A rigorous trial on the effectiveness of pharmacological interventions for preventing migraines in children and adolescents found amitriptyline and topiramate to be ineffective [15]. Such results may have led many clinicians to use nutritional supplements with fewer side effects, such as riboflavin, as an optional treatment before using drugs

[13][16]. Riboflavin continues to be used for migraine prophylaxis; however, the underlying mechanism of action is still unclear.

In order to better understand the relationship between migraines and riboflavin, this review focuses on the antioxidant and anti-inflammatory properties of riboflavin and mitochondrial damage. In addition, we summarize the current clinical evidence for riboflavin's efficacy on migraines.

2. Oxidative Stress in Migraines

Studies have indicated the involvement of oxidative stress in migraine pathogenesis and investigated various oxidative stress markers [17][18][19][20]. This review summarizes some of the representative oxidative stress markers and the antioxidant properties of riboflavin (**Table 1**).

Table 1. Summary of oxidative stress markers in migraineurs.

Markers	Design	Sample Size	Findings	Reference
Antioxidants (TAS), total antioxidant capacity (TAC), and total oxidants (TOS)	Case-control	75/65	Patients' serum TAS levels were significantly lower than those of healthy controls. Serum TOS values were significantly higher in patients than in control. The mean values of oxidative stress index (OSI) were greater in patients than in controls.	Alp et al., 2010 [20]
	Case-control	141/70	TAS, TOS, OSI had no statistical difference between the patients and controls.	Eren et al., 2015 [21]
	Case-control	50/30	No significantly different values of TAS, TOS, and OSI found in migraineurs.	Geyik et al., 2016 [22]
	Before and after	120/30	TAC levels were increased following transcranial magnetic stimulation and amitriptyline.	Tripathi et al., 2018 [23]
	Case series	32/14	Decreased serum TAC levels found in 37.5% of patients.	Gross et al., 2021 [24]
Peroxide and malondialdehyde (MDA)	Case-control	39/30	While migraine with/without aura patients had low platelet superoxide dismutase (SOD) concentrations, platelet SOD activity decreased only in migraine with aura patients.	Shimomura et al., 1994 [25]
	Case-control	56/25	The MDA levels of migraineurs were significantly higher than controls. The SOD activity was significantly higher in the	Tuncel et al., 2008 [19]

Markers	Design	Sample Size	Findings	Reference
			migraine with aura than migraine without aura. No significant correlation was found between these levels and headache attack duration.	
	Case-control	50/50	Migraineurs had significantly high MDA and “ferric reducing ability of plasma” levels compared to the other two groups (tension-type headache and control group).	Gupta et al., 2009 [26]
	Case-control	48/48	There was no significant difference in MDA concentration between migraineur and control groups. Significantly increased 4-hydroxynonenal levels were found in the migraine group compared to the control group.	Bernecker et al., 2011 [27]
	Case-control	32/14	In the migraine group, catalase was significantly lower and MDA concentrations were higher than controls. Serum catalase levels were significantly lower in migraineurs with deep white matter hyperintensities than in migraineurs without deep white matter hyperintensities and in controls	Aytaç et al., 2014 [28]
	Case series	32	High serum peroxide levels were found in 46.9% of patients.	Gross et al., 2021 [24]
8-hydroxy-2-deoxyguanosine (8-OHdG)	Case-control	50/30	Increased plasma 8-OHdG levels were shown in migraineurs.	Geyik et al., 2016 [22]
Alpha-lipoic acid (ALA)	Randomized controlled trial	44	In a within-group analysis, patients who received thioctic acid (ALA) for three months had a significant reduction in the frequency of attacks, number of headache days, and severity of headaches, while these outcomes remained unchanged in the placebo group. The proportion of 50% responders was not significantly different between thioctic acid (30.8%) and the placebo (27.8%).	Magis et al., 2007 [29]
	Before and after	32	The percentage of patients with a 50% or greater reduction in attacks was significantly reduced at 2, 4, and 6 months. The incidence rate ratio of attacks at 6	Cavestro et al., 2018 [30]

Markers	Design	Sample Size	Findings	Reference
			months was significantly decreased compared to the baseline.	
	Case series	32	Decreased serum ALA levels were found in 87.5% of patients.	Gross et al., 2021 [24]

A study of patients with migraines without aura showed decreased levels of total antioxidants (TAS), increased levels of total oxidants (TOS), and the oxidative stress index (OSI) compared with controls [20].

Summary of oxidative stress markers in migraineurs.

Dramatic metabolic changes in the cerebral cortex associated with intracellular calcium overload during CSD could induce transient oxidative stress [31][32]. CSD causes oxidative stress in the cerebral cortex, meninges, and even in the trigeminal ganglion, which is not directly exposed to the trigger substance [33]. Additionally, it suggests a direct stimulatory effect of reactive oxygen species (ROS) on nociceptor firing via transient receptor potential ankyrin subtype 1 (TRPA1) ion channels and an indirect role for ROS in sensitizing sensory afferents via the release of a major migraine mediator calcitonin gene-related peptide (CGRP) from nociceptor neurons [33]. TRPA1 ion channels enable CGRP release from dural afferents, and mediate the behavioral picture of neurogenic inflammation and migraines in animal models [34]. TRPA1 undergoes oxidative stress and initiates a neuroinflammatory response in migraines. In other words, TRPA1 might be a bridge between oxidative stress and neuroinflammation in migraines [34].

3. Mitochondrial Dysfunction

Mitochondria play an important role in a wide range of cellular functions, such as energy generation, ROS production, Ca 2+ homeostasis regulation, and apoptosis [35]. Mitochondrial disease symptoms occur in almost all organs, but primarily in high energy-consuming organs, such as the brain and muscles [35].

Interestingly, the seemingly unrelated migraine triggers, such as ovarian hormone changes, weather changes, alcohol, strong smells, strong light, and loud noises, have a potential common denominator in the form of changes in the mitochondrial metabolism and oxidative stress [36][37]. Disturbances in mitochondrial metabolism might contribute to the pathogenesis of migraines by lowering the threshold for migraine attack propagation [38][39]. Furthermore, mitochondrial genome analysis demonstrated that polymorphisms account for a significant portion of the genetic factors involved in migraine etiology [40], and clinical evidence of the link between migraine and mitochondrial dysfunction is slowly accumulating [2][41][42][43][44].

This current research showed that common migraine triggers have the ability to generate oxidative stress through mitochondrial dysfunction, calcium excitotoxicity, microglia and NADPH oxidase activation, and as a byproduct of monoamine oxidase (MAO), cytochrome P450, or NO synthase [36]. In particular, mitochondria are key to the primary mechanism of intracellular Ca 2+ sequestration; therefore, mitochondrial dysfunction can lead to pain

hypersensitivity [45]. Vasoconstriction during CSD is also triggered by an increase in Ca 2+ concentrations in the astrocytes through a process mediated by phospholipase A2, a metabolite of arachidonic acid [46]. Mitochondria play a crucial role in the normal functioning of neurons, and a Ca 2+ imbalance can lead to an imbalance in various downstream processes, and thus further increase susceptibility to migraines [3].

The migraine model demonstrated abnormalities in the mitochondrial biogenesis capacity of trigeminal neurons, with reduced copy numbers of mitochondrial DNA and altered mRNA levels of the peroxisome proliferator-activated receptor-γ coactivator 1-α [47], which are essential regulators of mitochondrial biogenesis [20]. These experimental findings indicate that mitochondrial dysfunction is an important hallmark of migraines.

4. Clinical Evidence of Riboflavin Efficacy

Seven studies (including three RCTs) in adults have evaluated the role of riboflavin in preventing adult migraines (**Table 2**). The dose of riboflavin was 400 mg, except in one case (100 mg) [11]. All studies demonstrated the effectiveness of riboflavin [9][11][48][49][50][51][52].

Summary of studies on riboflavin for pediatric migraines.

Study Design	N	Intervention	Comparison	Outcomes	Reference
RCT	48	Riboflavin (200 mg daily) for 12 weeks (n = 27)	Placebo for 12 weeks (n = 21)	No difference between the comparison groups in terms of the proportion of participants with 50% or greater reduction in migraine frequency (p = 0.125)	* MacLennan et al., 2008 [53]
Before-after study	41	Riboflavin (200 mg or 400 mg daily) for three, four, or six months	Baseline period	Significant reduction in headache frequency after treatment for three or four months (p < 0.01), which was not sustained at six months (p > 0.05)	Condo et al., 2009 [54]
Crossover RCT	42	Riboflavin (50 mg daily) for four months (n = 20)	Placebo for four months(n = 22)	No difference between the comparison groups in terms of change in migraine frequency (p = 0.44); the riboflavin group showed a greater reduction in the frequency of tension-type headaches than the placebo group (p = 0.04)	* Bruijn et al., 2010 [55]
RCT	98	Riboflavin (400 mg daily) for three months (n = 50)	Placebo for three months (n = 48)	Headache frequency decreased from the first month to the second month, and to the third month (3.7 per month); headache duration also	Athaillah et al., 2012 [56]

Study Design	N	Intervention	Comparison	Outcomes	Reference
				decreased (*p*-values: 0.012 and 0.001, respectively) compared to the placebo group. Disability, as measured by the PedMIDAS, also decreased ($p = 0.001$).	
RCT	90	Riboflavin (200 mg or 400 mg daily) for 3 months ($n = 30$, and 30, respectively)	Placebo for three months ($n = 30$)	The riboflavin 400 mg group showed a greater reduction in the headache frequency and duration than the placebo ($p = 0.00$ for both).	Talebian et al., 2018 [57]
Retrospective observational study	68	Riboflavin (10 or 40 mg daily) for three months ($n = 13$ and 55, respectively)	N/A	Significant overall reduction detected in the median frequency of headache episodes from baseline to three months ($p = 0.00$).	Yamanaka et al., 2020 [58]
Retrospective observational study	42	Riboflavin (100 and 200 mg for children weighing 20 to 40 kg and greater than 40 kg, respectively)	N/A	Significant decrease in the frequency of headache days after 2–4 months compared to the baseline. Mean headache intensity ($p < 0.001$), and headache duration ($p < 0.001$) decreased significantly.	Das et al., 2020 [59]

RCT, randomized controlled trial; MIDAS, Migraine Disability Assessment; N/A, not available. The asterisk (*) indicates a study with a negative result.

Summary of studies on riboflavin for adult migraine.

Study Design	N	Intervention	Comparison	Outcomes	Reference
Open label trial	44	Riboflavin 400 mg daily (23/44 received aspirin 75 mg daily)	N/A	A 68.2% improvement in migraine severity score, no difference between the aspirin-treated and non-aspirin-treated groups (*p*-value not reported)	Schoenen et al., 1994 [48]
RCT	55	400 mg daily	Placebo for three months ($n = 27$)	Riboflavin significantly reduced the frequency of seizures ($p = 0.005$) and the number of headache days ($p = 0.012$) when compared with the placebo group	Schoenen et al., 1998 [9]
Open label trial	26	400 mg daily vs. bisoprolol 10 mg daily or metoprolol 200 mg daily	N/A	Headache frequency was significantly reduced ($p < 0.05$) in both groups, but there was no difference between the two groups	Sándor et al., 2000 [49]

Study Design	N	Intervention	Comparison	Outcomes	Reference
Open label trial	23	400 mg daily	N/A	Headache frequency significantly decreased from 4 days/month at baseline to 2 days/month at three and six months ($p < 0.05$)	Boehnke et al., 2004 [50]
Open label trial	64	400 mg daily	N/A	62.5% responded and haplotype H was associated with a reduced probability of responding to riboflavin (OR, 0.24; 95% confidence interval [0.08, 0.71])	Di Lorenzo et al., 2009 [51]
RCT	100	100 mg daily for at least three months	Propranolol 80 mg daily for at least three months ($n = 50$)	A greater reduction in migraine frequency in the propranolol group at one month ($p < 0.001$), but no difference between the groups at three and six months	Nambiar NJ et al., 2011 [11]
RCT	90	400 mg/day	Sodium valproate 500 mg/day	The frequency, median duration per month, and severity of headache decreased in both groups, but the difference between them was not significant ($p > 0.05$). However, the vitamin B2 group had significantly fewer side effects ($p = 0.005$).	Rahimd et al., 2015 [52]

RCT, randomized controlled trial; N/A, not available.

Although no serious side effects have been reported to date, and there is a widespread perception that riboflavin has no side effects, some adverse effects have been reported. Studies utilizing high doses of riboflavin reported orange discoloration of the urine, polyuria, diarrhea, vomiting, and an increased appetite without weight gain [9][56][53][54]; studies using low doses did not report any adverse effects [58][55].

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