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Review

B2 or Not B2: A Systematic Literature Review on Migraine Headaches and Riboflavin Deficiency

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Abstract

Objective
To assess the prevalence of riboflavin deficiency in patients with migraines or headaches
Methods
Systematic review of the literature following the Preferred Reporting Items for Systematic
Reviews and Meta-Analyses guidelines.
Results
Two articles met the inclusion and exclusion criteria, and neither of these discussed riboflavin deficiency prevalence in those patients who suffer from migraines.
Conclusion
The prevalence of riboflavin deficiency in migraineurs and in headache patients is unknown.

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Introduction

Migraine, a disorder that subjects its victims to recurrent attacks of debilitating head pain, is the second leading cause of disability worldwide.[1] Migraines are often treated with different prophylactic medications including tricyclic antidepressants, antihypertensives, and vitamins and minerals. One specific nutrient that is recommended as a prophylactic is riboflavin, or vitamin B2. Numerous trials have demonstrated riboflavin's effectiveness as a migraine preventive.[2] According to one review on the topic, Vitamin B2 supplementation can reduce the frequency and duration of migraine attacks without incurring serious side effects.[2] The World Health Organization considers riboflavin to be a necessary vitamin for life[3], because it is utilized in the creation of two major coenzymes - flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN or riboflavin-5'-phosphate). These coenzymes are necessary components of metabolism for steroids, drugs, and fatty acids, and play a major role in energy production.[4-6]

While the exact mechanism of riboflavin's efficacy as a migraine preventive is unknown, it is safe to assume that riboflavin would have a greater preventive effect in patients with riboflavin deficiency, especially considering that patients with riboflavin deficiency are well known to experience headaches.[6,7] One proposed mechanism for the role is the effect that low B2 levels have on the mitochondrial energy harnessing apparatus and how with low levels this is harmed. However, the pieces in which this leads to migraine symptoms still remains unknown.[2] The research question at hand is, "What is the prevalence of riboflavin deficiency in patients with migraines or headaches?" Here, we create a systematic literature review on what is currently known about the prevalence of riboflavin deficiency and its relationship to the presence of migraines or headaches.

Materials and Methods

This literature review was performed following the standardized methods of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) as defined by Moher et al.,[8] In the creation of this particular review, we utilized similar methodology to that of Tremmel et al.,[9] in their literature review on obesity.

Results

Search Strategy

Relevant articles were identified via a systematic search of various databases performed on 11.5.2022. The three databases utilized were PubMed, Cochrane, and Google Scholar. To help ensure results are easy to reproduce, the search parameters are included below:

Google Scholar: Results published on/before 11.5.2022. Search terms were: 1) "riboflavin deficiency" and "migraine", 2) "riboflavin deficiency" and "headache", 3) "B2 deficiency" and "migraine", 4) "B2 deficiency" and "headache". There was a total of 449 non-duplicate results found on Google Scholar. All articles were included in the initial search and then reviews were filtered out manually.

Cochrane: Results published on/before 11.5.2022. Search terms were: 1) "riboflavin deficiency" and "migraine", 2) "riboflavin deficiency" and "headache", 3) "B2 deficiency" and "migraine", 4) "B2 deficiency" and "headache". There was a total of 4 non-duplicate results found on The Cochrane Library.

PubMed: Results published on/before 11.5.2022. Search terms were: 1) "riboflavin deficiency" and "migraine", 2) "riboflavin deficiency" and "headache", 3) "B2 deficiency" and "migraine", 4) "B2 deficiency" and "headache". There was a total of 12 non-duplicate results found on Pubmed.

Secondary Search Strategy

Following the initial search strategy performed on 1.14.2023, an additional search criterion was determined to be of importance, ariboflavinosis. An additional search using this term was performed on 1.14.2023.

Relevant articles were pulled via a systematic search of various databases performed on 1.14.2023. The three databases that were utilized were PubMed, Cochrane, and Google Scholar. Search parameters are included below:

Google Scholar: Results published on/before 1.14.2023. Search terms were: 1) "ariboflavinosis" and "migraine", 2) "ariboflavinosis" and "headache". Utilizing this search strategy a total of 136 unique articles were found on Google Scholar.

Cochrane: Results published on/before 1.14.2023. Search terms were: 1) "ariboflavinosis" and "migraine", 2) "ariboflavinosis" and "headache". Utilizing this search strategy a total of 0 unique articles were found on the Cochrane Library.

PubMed: Results published on/before 1.14.2023. Search terms were: 1) "ariboflavinosis" and "Migraine" (12), 2) "ariboflavinosis" and "headache". Utilizing this search strategy a total of 8 unique articles were found on PubMed.

Inclusion and Exclusion Criteria

Articles were assessed using the following inclusion criteria: (1) Articles must be written in English; (2) full-text copies of the studies were available via open-access or

through library access via an affiliated organization; (3) studies were written and published before 11.5.2022, or in the case of ariboflavinosis, before 1.14.2023. Exclusion criteria included: (1) Studies not discussing B2, riboflavin deficiency, or ariboflavinosis; (2) studies not discussing migraines or headaches; (3) articles that were not in peer reviewed journals; or (4) review articles.

Selection and Data Extraction

Two authors (T.V. and J.F.) both independently analyzed all three databases for potential articles. Initial screening involved reading the title and abstract of each potential articles and comparing it to the criteria listed above. Lists were screened for potential duplicates and these duplicate articles were removed in accordance with the PRISMA Guidelines[8]. The authors then compared individual lists of potentially acceptable articles, challenging each other until a single, agreed-upon list was formulated and developed into an Excel spreadsheet. Remaining articles upon which the authors could not agree on were brought to a third author (J.T.) for review and were included or excluded based on his judgment. Replace with Figure 1 illustrates each step of the review process, along with how many papers were eliminated at each phase. Figure 2 demonstrates the secondary search strategy performed on January 14, 2023.

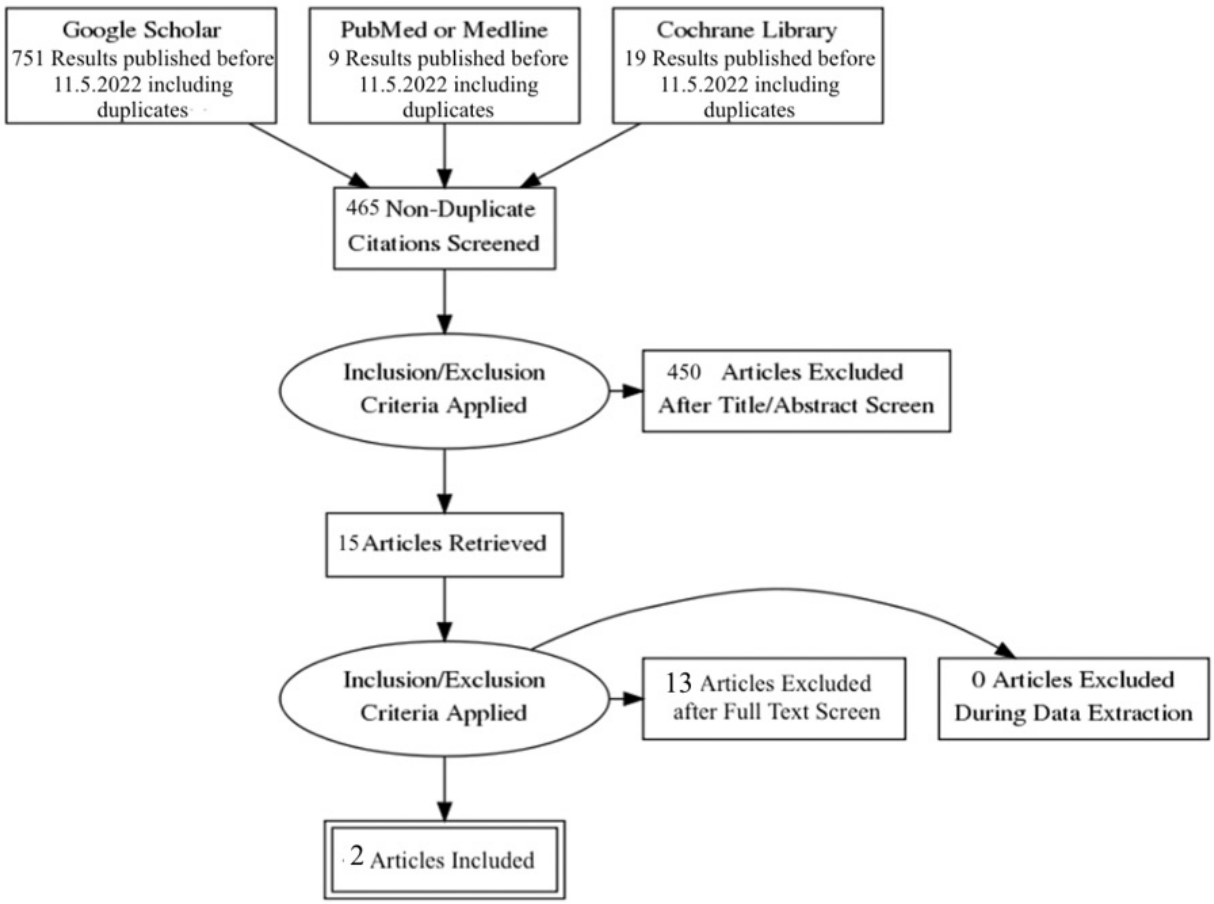

Figure 1. PRISMA Flowsheet with number of papers eliminated at each step of the process on November 5, 2022

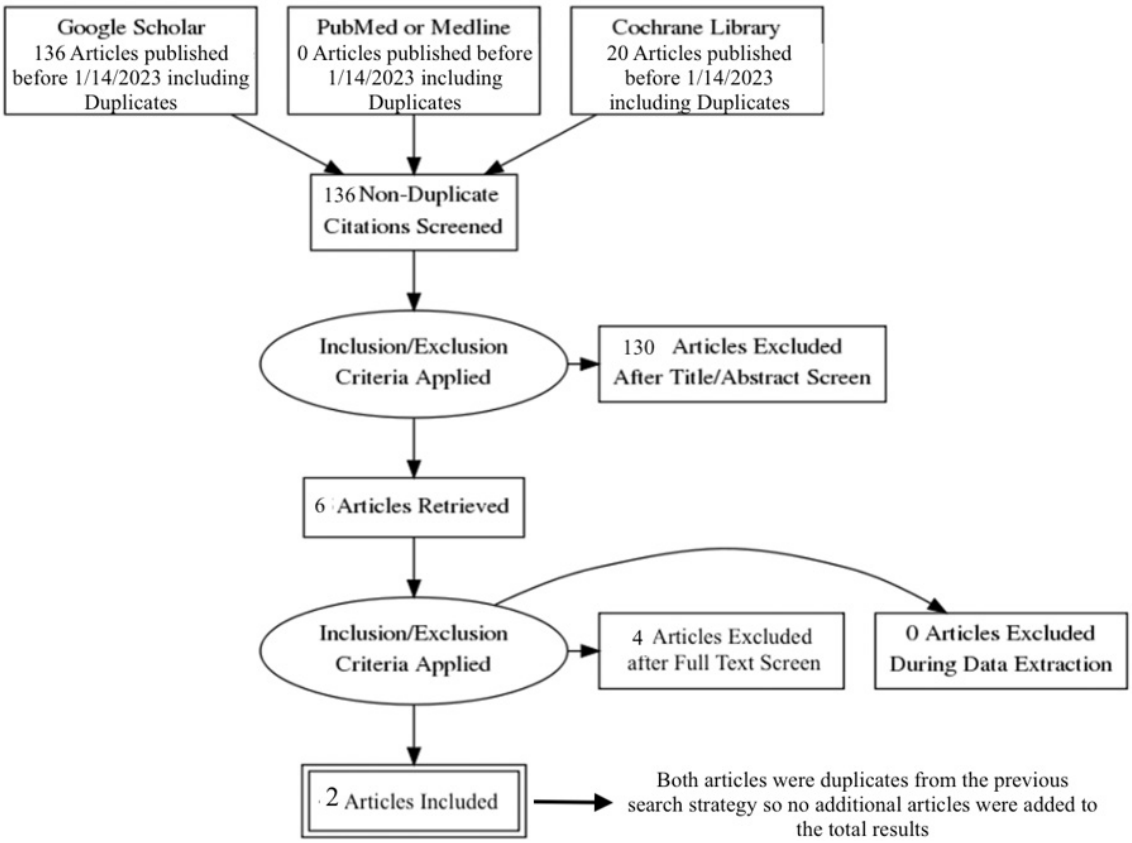

Figure 2. Secondary search strategy performed on January 14, 2023

Results

The major results of this particular systematic review are contained within Table 1, Table 2, and Table 3. Through the systematic process, only two articles were found via the secondary search described above. Tables 1 and 2 below contains further information about the two articles.

Tables 2 and 3 are validated tools for the assessment of studies that have been put out by the National Institutes of Health (NIH)[10]. These tools set standards created by the NIH and have been created with a number of different study types in mind including observational cohort and cross-sectional studies and non-randomized studies. Utilizing the criteria that the NIH placed for choosing each of the tools, based on the study type one author, TV, filled out these and then sent the filled out tools to the other authors. Because the two studies were different in nature, two different assessment tools were utilized based on the validated criteria provided by the NIH. Discussion was had between the three authors following this in regard to the way that it was filled out and any discrepancies were discussed at length and then changed based on consensus.

Table 1. Breakdown of the Articles Selected for the Systematic Review

Authors	Title	Topic(s) Tested	Study Size	Groups	Results	Risk of Bias
Li, Huilun; Krall, Jenna R.; Frankenfeld, Cara; Slavin, Margaret	Nutritional Intake of Riboflavin (vitamin B2) and migraine: a cross-sectional analysis of the National Health and Nutrition Examination Survey (NHANES) 2001-2004 [14]	Riboflavin consumption and the prevalence of migraines	n = 3,439 participants, ages 20-50	Within-group and between-group designs. 2,604 in control group and 835 in migraine group. Data on the occurrence of migraine was self-reported.	With dietary third quartile (Q3) used as reference group (2.07-2.87 mg/day), both dietary Q2 and Q4 (Highest total intake) were significantly different. For total riboflavin consumption, odds of migraine were 25% lower in Q2 (1.63-2.57 mg/day) vs. Q1 (0-1.45 mg/day) overall, and, among males, 36% lower in Q2 (1.87-2.83 mg/day) vs. Q1 (0.16-1.87 mg/day). Elevated dietary consumption of riboflavin (2.07-2.87 mg/day) was associated with reduced odds of migraine, which is lower than the levels administered in previous supplementation trials.	Low risk based on the bias risk assessment in Table 2. The survey data that was collected had low risk for potential discrepancies between the biological sexes due to the large and inclusive data set.
Smith, Clifford	The Role of Riboflavin in Migraine [15]	Prevention of migraine through daily riboflavin supplementation. Also, cessation of active migraine following riboflavin supplementation	n = 19 (15 female, 4 male) (15 with "simple migraines," 4 with "ophthalmic migraines")	Within-Group design - results were self-reported (Sub groups of "ophthalmic migraines" and "simple migraines")	42% prevented an oncoming attack with 5-6 hourly doses of 5mg. 42% discontinued treatment after migraines ceased; 38% of those experienced recurrence, but prevented further attacks by resuming therapy. 100% reported improvement in general well-being. The patients reported resolution in migraines in all with "ophthalmic migraine." In those patients with "simple migraine," the use of riboflavin resulted in 67%, decreased in frequency and severity in 20% of the patients, and 7% of the patient experienced some improvement in their symptoms despite some noncompliance.	Moderate to High based on the bias risk assessment in Table 3. One area of potential bias is the large difference between the biological sexes. There was a large discrepancy between the biological sexes studied in this study with a near 3:1 ratio of females to males. This, however, might be related to the biological differences actually seen. There is a higher incidence and prevalence of migraine HA in females than males, which it may promote bias against female migraine sufferers, but can also be viewed as a microcosm of the larger population of migraine sufferers.

Table 2. The National Institutes of Health (NIH) quality assessment tool for observational cohort and cross-sectional studies [13] for Nutritional Intake of Riboflavin (vitamin B2) and migraine: a cross-sectional analysis of the National Health and Nutrition Examination Survey (NHANES) 2001-2004

Major Components		Response options	
1. Was the research question or objective in this paper clearly stated?	**Yes**	No	Cannot Determine/ Not Applicable/ Not Reported
2. Was the study population clearly specified and defined?	**Yes**	No	Cannot Determine/ Not Applicable/ Not Reported
3. Was the participation rate of eligible persons at least 50%?	**Yes**	No	Cannot Determine/ Not Applicable/ Not Reported
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	**Yes**	No	Cannot Determine/ Not Applicable/ Not Reported
5. Was a sample size justification, power description, or variance and effect estimates provided?	**Yes**	No	Cannot Determine/ Not Applicable/ Not Reported
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Yes	No	Cannot Determine/ **Not Applicable**/ Not Reported
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Yes	No	Cannot Determine/ **Not Applicable**/ Not Reported
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	**Yes**	No	Cannot Determine/ Not Applicable/ Not Reported
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	**Yes**	No	Cannot Determine/ Not Applicable/ Not Reported
10. Was the exposure(s) assessed more than once over time?	Yes	No	Cannot Determine/ **Not Applicable**/ Not Reported
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	**Yes**	No	Cannot Determine/ **Not Applicable**/ Not Reported
12. Were the outcome assessors blinded to the exposure status of participants?	Yes	No	**Cannot Determine**/ Not Applicable/ Not Reported
13. Was loss to follow-up after baseline 20% or less?	Yes	No	Cannot Determine/ **Not Applicable**/ Not Reported
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Yes	No	Cannot Determine/ **Not Applicable**/ Not Reported
Quality Rating	**Good**	Fair	Poor

Table 3. Checklist for quality assessment of non-randomized studies (comparative and cohort studies) [14]

Criteria	Yes/No/Unclear
1. Were participants a representative sample selected from a relevant patient population (e.g. randomly selected from those seeking treatment despite age, duration of disease, primary or secondary disease and severity of disease)?	No
2. Were the inclusion/exclusion criteria of participants clearly described?	Yes
3. Were participants entering the study at a similar point in their disease progression (i.e. severity of disease)?	Yes
4. Was selection of patients consecutive?	No
5. Was data collection undertaken prospectively?	Yes
6. Were the groups comparable on demographic characteristics and clinical features?	Yes
7. Was the intervention (and comparison) clearly defined?	Yes
8. Was the intervention undertaken by someone experienced at performing the procedure?	Yes
9. Were the staff, place and facilities where the patients were treated appropriate for performing the procedure (e.g. access to back-up facilities in hospital or special clinic)?	Yes
10. Were any of the important outcomes considered (i.e. on clinical effectiveness, cost-effectiveness, or learning curves)?	Yes
11. Were objective (valid and reliable) outcome measures used, including satisfaction scale?	No
12. Was the assessment of main outcomes blind?	No
13. Was follow-up long enough (≥ 1 year) to detect important effects on outcomes of interest?	
No	
14. Was information provided on non-respondents, dropouts?	Unclear – the study did not mention non-respondents or drop outs, only the level of amelioration of migraine symptoms in the patients studied.
15. Were the characteristics of withdrawals/dropouts similar to those that completed the study and therefore unlikely to cause bias?	Unclear
16. Was length of follow-up similar between comparison groups	No
17. Were the important prognostic factors identified (e.g. age, duration of disease, disease severity)?	No
18. Were the analyses adjusted for confounding factors?	No

Discussion

This particular study looked to see what the current literature suggested about the prevalence of migraines or headaches with vitamin B2 (riboflavin) deficiency. In examining the two articles that were obtained through the search strategy, a few major similar points were made. First, those with increased intake of riboflavin had decreased odds of having a migraine. This is important as riboflavin supplementation is one of several natural recommendations in the treatment of migraine headache disorder. Therefore, if in the natural diet, there is already an increase in the amount of riboflavin, these individuals by nature of their diet are already preventing further migraine headaches. Second, the number of migraine events is based only on the self-reported data of the symptoms of each patient, not true objective data. This becomes clinically relevant as migraine headaches are difficult to parse out and without objective data, clinicians must rely on history taking skills and efforts to better hear what their patients are saying or trying to convey in order to better understand the semiology of the headache and the associated features in order to better treat the patient – especially if they have true migraine headache disorder like that seen in this study population.

Some minor take away points from the Smith (1946)[11] Article included that 100% (4/4) of the ophthalmic migraine group had complete relief of their migraine symptoms, which is interesting despite the extremely limited sample size of those suffering from ophthalmic migraines. This could imply that the symptomatology of the migraine headache (such as ophthalmic migraines versus vestibular migraines) might determine the responsiveness to treatment with B2 supplementation. However, with such a small sample size, such conclusions are hard to make. Ophthalmic migraines (also known as retinal migraines or ocular migraines) are defined as a transient loss of vision in one eye that is associated with a migraine headache.[11] While this particular paper made the case that riboflavin played a role in the treatment of migraine disorder and mentioned riboflavin deficiency as a potential mechanism for the etiology of migraine headaches, it did not truly test for riboflavin deficiency, but instead focused on the treatment of migraine headaches with riboflavin replacement therapy. This paper did not provide further details or data analysis beyond simple reporting of the percentage of participants that responded to the treatment, the percentage of participants that stopped after amelioration of symptoms, the percentage of participants who experienced recurrences after cessation of Vitamin B2 supplementation, and the percentage of participants who experienced improvements in general well-being (which in the study was not defined). The follow up for the patients was only reported in this study if they stopped taking the Vitamin B2 supplementation or if they had recurrence of symptoms after stopping the Vitamin B2 supplementation. The study in and of itself was very small with a sum total of 19 participants as detailed in Table 1. Some of the major limitations of this particular article included small sample size, a lack of true data/analysis or protocol, and lack of uniformity for follow up with patients. Additional limitations included no "uniformity of complaints" for the simple migraine group (this statement of the lack of uniformity of complaints was directly from the paper cited and further clarification was not provided in the actual paper), and an unclear duration of treatment as some patients were able to stop the treatment completely without problems, while others reported a return of symptoms after discontinuation of their vitamin B2 supplements which limits the applicability of the study in both reproducibility and the rationale as to why it works. Lastly, there was a large discrepancy between the biological sexes studied in this study with a near 3:1 ratio of females to males. This, however, might be related to the biological differences actually seen. There is a higher incidence and prevalence of migraine HA in females than males, which it may promote bias against female migraine sufferers, but can also be viewed as a microcosm of the larger population of migraine sufferers.

The Li et al.[12], conversely had a very large sample size and had a number of exclusions, which limited the generalizability of the study. Specifically, this study left out patients with diabetes or alcoholism because these disease states can lead to riboflavin deficiency. While this limited the number of participants, the sample size was still large with a control group that was much larger than the group which was affected by migraines. Alcohol intake, caffeine intake, and poverty:income ratio data were categorized into groups to minimize the influence of outliers. The likely reason that the poverty:income ratio data was included was to approximate access to nutritious foods that would contain the necessary vitamin content to provide appropriate levels of Vitamin B2 necessary for healthful living. Nevertheless, the reason that the poverty:income ratio data was included is not explicitly stated in the paper cited. One key take away that this study demonstrated was a difference between dietary and total intake of riboflavin. Dietary riboflavin being the amount consumed in normal meals and total intake including both dietary and additional supplementation from vitamin and mineral supplements or prescription grade medications. Dietary riboflavin consumption seems to be an important consideration as current research tends to focus on the

use of riboflavin supplements, instead of looking at total intake. One of the most important conclusions from this paper was that the effective dose of riboflavin for migraine prophylaxis may be far lower than levels indicated by previous trials, with such information potentially changing the current recommendation in the use of this supplement in the treatment of migraines.

Limitations

As with any systematic review paper, there are several limitations which can be encountered. The first and foremost is that this paper is a snapshot in time with the end point in November of 2022 or January of 2023. There may have been other research performed in the last several months that conclusively provided insight into this disease process at a cellular or a molecular level which was not encountered by the research team. Other limitations include lacking access to a number of other non-publicly accessible databases and repositories for articles which may have in part limited the number of articles which were included in the literature review. Between the two articles eventually included, specifics into the similarities or differences between the biological sexes for disease severity were not discussed, nor was the prevalence of B2 deficiency between the biological sexes. The last major limitation was the number of eventual articles included in the final review. Because of the stringent requirements placed by the literature review to only include those articles which specifically discussed riboflavin deficiency, there were only two articles eventually included.

Future Research Directions

There currently is no data on the prevalence of riboflavin deficiency in patients with migraines and/or headaches. Because of the use of riboflavin as a migraine preventative it is imperative, based on our literature review, that a study be carried out utilizing either a survey or chart review of patients based on current serum riboflavin levels before using riboflavin as a preventative treatment for migraines. Such data will enable a link to be drawn, if it exists, for certain patient populations, allowing for better and more specific treatments to be utilized for patients suffering from both migraine and nonmigraine headache. Such targeted treatments may improve quality of life, and potentially cure those suffering from ariboflavinosis-related migraines, allowing for a more dietary/natural treatment instead of symptomatic coverage. Lastly, further explorations into the differences or similarities between the biological sexes for disease severity and the prevalence of B2 deficiency between the biological sexes should be examined in detail in order to ensure that these that these differences, if any, are not overlooked.

Conclusions

The current literature is severely lacking in regards to an understanding of the incidence and prevalence of those who suffer from headaches or migraines and their relative vitamin B2 status. While there remains the recommendation for the use of riboflavin as a preventative medication in those suffering from migraines, there continues to be a large lack of information as to the mechanism by which this works. Because of the current leading theory that vitamin B2 deficiency can lead to mitochondrial dysfunction which then in part leads to the development of the symptoms[2], this might lead the provider to believe that the improvement in migraine headache with supplementation of vitamin B2 might be secondary to the correction in the deficiency in this vital nutrient. It is the recommendation of the authorial team, secondary to this lack in the literature, that further studies be carried out in those populations of patients suffering from migraines to evaluate for potential deficiency syndromes which might be remedied with the use of riboflavin supplementation either in the diet, or with vitamin supplementation to improve their symptoms and potentially cure the patient's condition.

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