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The Most Effective Dose of Riboflavin Supplementation to Reduce EGR-AC Levels in Different Age/Gender and Duration Subgroups: A Systematic Review and Meta-Analysis

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Abstract

It has been reported that the erythrocyte glutathione reductase activation coefficient (EGR-AC) corresponds to the antioxidant activity of riboflavin. It is found that riboflavin supplements decrease EGR-AC. The aim of this systematic review is to determine the most effective doses of riboflavin supplementation to reduce EGR-AC levels in different age, gender and duration subgroups. A systematic search of relevant articles was performed on the PubMed, Scopus, Science Direct, and Google Scholars from inception to April of 2019. The clinical trials which administered riboflavin as an intervention were included. The mean and standard deviation of the main outcome (EGR-AC level) in intervention and placebo groups were considered for analysis. A total of 44 studies were identified and 10 studies were eligible. In total 362 subjects were enrolled into this study. The data of the EGR-AC level (WMD: - 0.38; 99.9% CI, -0.39 to -0.38; P<0.001) were compared between intervention and placebo groups. It was found that the most effective supplementation dosages of riboflavin to reduce the EGR-AC level were 2 mg, 4 mg, and 5 mg daily. Higher or lower doses only had a minor or no effect on EGR-AC level. Moreover, the results showed that the potential doses (2-5 mg of riboflavin supplementation daily) have more effect on reducing the EGR-AC level in female than males. In Conclusion, this meta-analysis revealed that 2-5 mg/daily of riboflavin supplementation (for 48,6,8 and 12 weeks, respectively) is the most effective dose to reduce the EGR-AC levels in two subgroups of male/female subjects.

Keywords: Erythrocyte glutathione reductase activation coefficient • Riboflavin supplementation • Dose • Clinical trials

Introduction

Riboflavin (vitamin B2) is a water-soluble vitamin which is essential for human health, being found in a wide variety of foods. Studies showed that in UK, 95% of adolescent girls and 75% of young women have insufficient riboflavin status, with riboflavin deficiency among 49-78% of elderly population, which is a health concern. Riboflavin plays an eminent role in metabolic functions in mitochondria by mediating the transportation of FAD and Flavin Adenine Mononucleotide (FMN); hence, suboptimal riboflavin intake causes many mitochondrial metabolism disorders. According to the animal studies, riboflavin deficiency results in weight gain and fatty liver. An adequate riboflavin intake improves the integrity of cellular membranes. Moreover, it may protect the body against oxidative stress. For the first time, we have claimed that riboflavin can be considered as an potential antioxidant. That is why that suboptimal status of riboflavin can lead to the progress of oxidative stress related diseases such as the cataract or cancer. Riboflavin plays a role in many enzymatic reactions in the human body such as glutathione reductase. It is converted to Flavin Adenine Dinucleotide (FAD), which is an active form of riboflavin. Adequate accessibility of FAD induces the activity of Glutathione Reductase (GR); therefore, a low intake of riboflavin decreases the GR activity [1].

As a water soluble vitamin, the concentration of riboflavin in the RBC and urine is an appropriate biomarker of riboflavin short-term intake while Erythrocyte Glutathione Reductase Activation Coefficient (EGR-AC) assay is considered as a long term and well-established method of riboflavin status. The EGR-AC indicate the availability of the FAD cofactor for GR in RBC. The EGR activity coefficient is defined as the activity of glutathione reductase with FAD divided by the activity of glutathione reductase without FAD. Furthermore, the EGR-AC determines the riboflavin status of tissue in the long-term, and its level decreases following the riboflavin supplementation. It is assumed that some doses of riboflavin supplementation are more effective than other dosages. There is no meta-analysis for effective

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dosage of riboflavin in human. This study has investigated the effect of different riboflavin supplementation dosages on the EGR-AC level in age, gender and duration subgroups. Therefore, this study was aimed to determine the most effective dosage of riboflavin supplementation to reduce EGR-AC levels.

Materials and Methods

Search strategy

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol. A systematic search of relevant articles was performed in the PubMed, Scopus, Science Direct, and Google Scholars from inception to April of 2019. The keywords used for the search strategy included "vitamin B2", "vitaminB2", "vitamin B 2", "riboflavin", "vitamin G", "glutathione reductase", "glutathione reductase activity", "glutathione reductase level", "EGR-AC", "ACEGR", "EGR-AC level", "EGR-AC", and "EGRAC". Moreover, the reference lists of the relevant articles and systematic reviews were screened to avoid missing any study. All studies found from electronic databases and reference lists were transferred into the EndNote software [2].

Selection criteria

All controlled Randomized Clinical Trials (RCTs) with placebo/control groups evaluating the relationship/effect of riboflavin supplementation with/on the EGR-AC level were included. No country restriction with English language was applied. Animal or cell culture experiments, editorials, commentaries, review articles, case reports, and articles lacking a placebo or control group were also excluded. Studies in which riboflavin was supplemented in the combination with other nutrients were also excluded. The full texts of the selected articles were prepared and used to extract the data and articles based on the PICOS criteria (Table 1).

Parameter	Population	Intervention	Comparator	Outcome	Study design
Criterion	Human (all age groups)	Riboflavin	Placebo	Effect on EGR-AC level	RCT

Table1: PICOS criteria for the inclusion of studies.

Data extraction and quality assessment

Data extracted from RCTs included the sample size of each group, age, gender, publication year, riboflavin dosage, supplementation type, duration of intervention, and mean of EGR-AC in intervention and control groups before and after the intervention [3]. The quality of each article was assessed using the specific criteria outlined in the COCHRANE for clinical trials as shown in the RevMan-5 software (Figure 1).

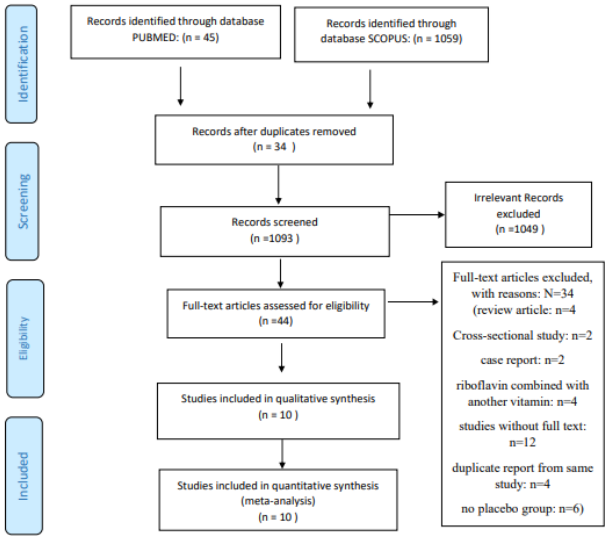

Figure1: RevMan-5 software for risk of bias assessment of included studies.

Statistical analysis

The data presented as the Weighted Mean Difference (WMD) and Standard Deviation (SD) of the main outcome (EGR-AC level) in the intervention and placebo groups were considered for analysis. To examine statistical heterogeneity across the studies, a c2 test was employed on (n-1) degrees of freedom. An I2 value <25%, about 50%, and >75% indicated a low, moderate, and high heterogeneity, respectively. Subgroup analysis was conducted to identify the causes of between-study heterogeneity or the effects of different parameters on the effect size. Potential clinical sources of heterogeneity were assessed according to the following categories: mean of age, dosage of riboflavin supplementation, health status of subjects, adjustment for confounding factors and study quality. Potential publication bias was assessed using the Begg's and Egger's regression model. The STATA statistical software version 12.0 was employed for data analysis. P-values less than 0.05 were considered as significance.

Results

Selection and characteristics of included studies

Out of 1104 identified studies in the first round of screening, 1093 studies remained after the exclusion of duplicates. Furthermore, 1049 studies were excluded for one of the following reasons: irrelevant data or lack of riboflavin supplementation or EGR-AC data, non-human studies, chemistry or cell line studies, editorial, commentary, review article, cross-sectional studies, and case reports. In the next round, full-text screening led to the exclusion of 34 articles due to their inadequate data. Finally, 10 clinical trials were found to be eligible for inclusion in the meta-analysis (Figure 2). The recommended riboflavin dosage ranged from 1.3 mg/day to 60 mg/day and the duration of treatment was between 3 and 48 weeks. The type of intake was oral supplementation.

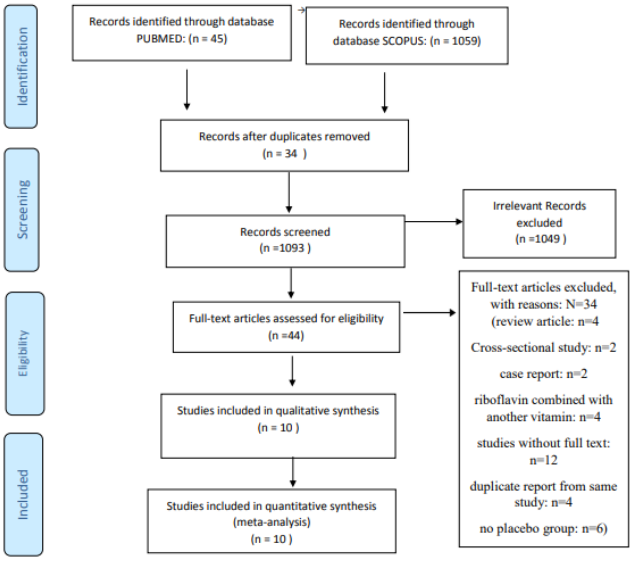

Figure2: Literature search and study selection process for inclusion in a meta-analysis of riboflavin supplement and EGR-AC level.

Characteristics of included studies

The included articles were published between 1984 and 2013. A total number of 363 patients were enrolled in the interventional studies. The participants were selected from different countries (Northern Ireland, United Kingdom, United Arab Emirates, Canada, Portugal, Ireland, Gambia, India, and Iran) with an age range of 9-78 years. These 10 clinical trials examined whether riboflavin supplementation decreases the EGR-AC level in patients. The quality score of each clinical trial was determined using the RevMan-5 software (Figure 2).

Subgroup analysis

Initial analysis of studies investigating the effect of riboflavin on the EGR-AC level in case and control groups, before and after the intervention is shown in Figure 3. In the second round, the effect of different riboflavin dosages was evaluated in three gender subgroups including group 1 (male), 2 (female), and 3 (male/female). In the third round, the effect of different riboflavin dosages on EGR-AC were evaluated in all age and gender groups, followed by subgroup analysis by age including children (0-14 years old), young aged (15-24 years old), adults (25-65 years old) and older people (above 65 year old). Also, performed an analysis based on duration of studies (3-48 weeks) [4].

A scatter plot was generated to show the trend of dosage effectiveness before and after the riboflavin supplementation and the effectivness of riboflavin supplementation on the change of EGR-AC before and after the supplementation in intervention group compared to placebo group shown in Figure 4.

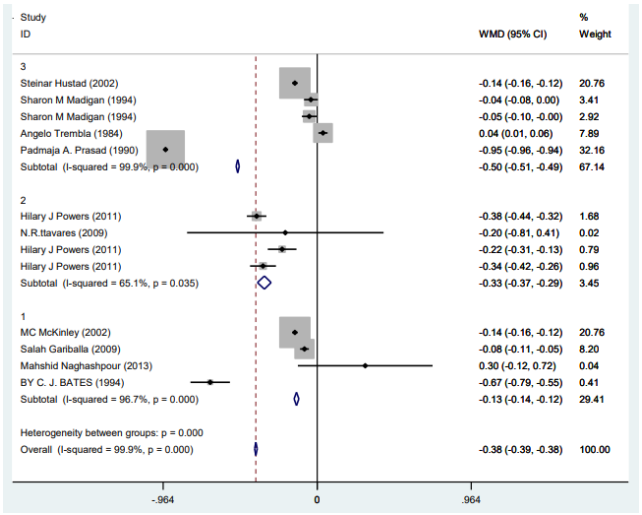

Figure3: Forest plot of weighted mean difference (WMD) in EGR-AC level with riboflavin supplementation in subgroup by gender. 1: male, 2: female, 3: both.

Finally, the results showed that the most effective doses of riboflavin supplementation to reduce EGR-AC levels were 2 mg, 4 mg, and 5mg daily. Higher or lower daily doses such as 1.3 mg, 1.6 mg, 10 mg, 25 mg, or 60 mg of riboflavin supplementation had only a limited effect on reducing the EGR-AC level. Therefore, 2-5 mg is concluded as the most effective dose of riboflavin supplementation to reduce the EGR-AC levels. Moreover, it was found that the effective doses had more effect on the reduction of EGR-AC levels in females compared to males. According to the age subgroups, the most effective range of dosage (2-5 mg daily) was more effective among young (15-24 years old) and adult patients (25-65 years old) compared to the other age subgroups. Furthermore, in subgroup by duration of studies; the most effective durations were observed in 48, 6, 8 and 12 weeks, respectively. In fact, in all this duration. The patients were intook 2-5 mg of riboflavin. When excluding the age, the heterogeneity analysis was calculated as I^2 value which is -0.38 (99.9% CI, -0.39 to -0.38; P<0.001). However, after the inclusion of the age, heterogeneity was 73.7%. Egger test with 95% CI was between -15.5824 and 39.76563 (P= 0.357).

Figure 8.

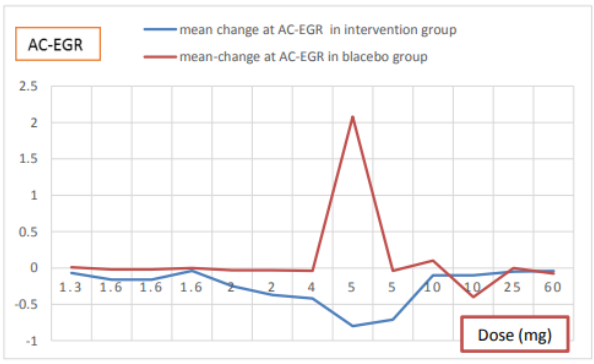

Figure4: Change at EGR-AC level by supplementation of different dosages riboflavin in comparison baseline with final.

Discussion

A balance diet provides 1.4 mg/day of riboflavin which is almost equal to the recommended daily allowance (RDA for riboflavin, which is 1.2-1.3 mg daily). Riboflavin is found in variety of foods such as dairy products, eggs, meats, and some green vegetables. Moreover, gut microbiota produces tiny amounts of riboflavin. Riboflavin deficiency causes anaemia, macronutrient metabolism disorders, sore throat, inflamed mucous membranes, cataract development, photophobia, and migraine headaches. EGR-AC is considered as a long-term assessment tissue saturation for riboflavin status in vitro which is inversely related to glutathione reductase (GR) levels. Lower the EGR-AC level is linked to a higher antioxidant activity of riboflavin. GR is an important enzyme involved in the regulation and maintenance of cellular redox homeostasis by re-reducing the oxidized glutathione to reduced glutathione. Glutathione itself reduces molecules via reducing the thiol residues. This anti-oxidation effect of glutathione is one of the main mechanisms by which riboflavin exerts its anti-oxidation property, which is first claimed by us previously. The result of current systematic review and meta-analysis demonstrates that riboflavin supplementation at the doses of 2-5 mg daily could significantly decrease the EGR-AC level compared to the lower and higher doses. Furthermore, it was found that riboflavin supplementation had a significant effect on the EGR-AC level in young people compared to the elderly [5].

Interestingly, it is also found that the most of the studies used the non-effective doses of riboflavin (out of the range of 2-5 mg daily) for elderly population they studied on. Comparing the results in gender subgroups, it is found that the female population showed a better response riboflavin supplementation compared to the males. Also, consider to duration of studies, the most effective seen when patient's consumed 2-5 mg of riboflavin. Tavares et al used the same supplementation dose of 10 mg and reported a small decrease of Homocysteine (Hcy) and C-Reactive Protein (CRP) concentration with no effect on ferritin or folate levels. MC McKinley et al performed a study in 2002 with lower dosages (1.6 mg daily) of riboflavin for 12 weeks on Hcy concentration, and they concluded no significant change on Hcy and EGR-AC level. A study on free-living elderly people using almost high and low dosage of riboflavin and reported that 25 mg riboflavin is more effective than 1.6 mg on the levels of EGR-AC. The probable reason for this can suboptimal riboflavin status of the population studied. The results showed no gender difference in the EGR-AC level before and after the intervention. However, comparison of the 45% variance of EGR-AC in this study with the results of other studies suggests that the effect of riboflavin supplementation at a dose of 1.6 mg is not significant compared to 2 mg, 4 mg, and 5 mg. Furthermore, the reason for this variance could be riboflavin deficiency of these aged patients. Powers et al found that the EGR-AC level has a greater reduction at the doses of 2 mg and 4 mg in a study performed in young women with marginal riboflavin deficiency, which is in the same line with our findings. These studies confirm that lower or higher doses of riboflavin (out of the range of 2-5 mg daily) not only effective to change the EGR-AC level, but also they are not effective to change other biomarkers in human body. It seems that the dosage of riboflavin supplementation to achieve optimal results varies in different population age, gender and duration subgroups. Moreover, riboflavin supplementation may have a better result among patients with suboptimal riboflavin levels compared to those with optimal levels.

Conclusion

This systematic review and meta-analysis study showed that the riboflavin supplementation dosage at the range of 2-5 mg daily for 48, 6, 8 and 12 weeks is the most effective dose to decrease EGR-AC levels. Other lower or higher doses have not a significant effect on EGR-AC levels. Furthermore, it was found that riboflavin supplementation had a significant effect on the EGR-AC level of young people compared to the elderly. Also, comparing the results in gender subgroups, it is found that the female population show a better response to riboflavin supplementation compared to the males.

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Authorship

M.GH and A.S designed the research, wrote the manuscript, performed the literature search and designed the scatter plots. M.GH analyzed the data conducted the statistical analysis. All authors read and approved the final manuscript.

Declaration of Interest

The authors (M.GH and A.S) have no relevant interests to declare.

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