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ORIGINAL

IMPACT OF VITAMIN D AND B6 SUPPLEMENTATION ON PHYSICAL FITNESS AND GAME PARTICIPATION IN ADOLESCENTS WITH PREMENSTRUAL SYNDROME: A META-ANALYSIS

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ABSTRACT

Introduction: This meta-analysis investigates the effects of Vitamin D and Vitamin B6 supplementation on premenstrual syndrome (PMS) in adolescents, with a specific focus on their impact on physical fitness and participation in games and sports. **Methodology:** A comprehensive literature searches up to March 2022 identified 11 trials involving 1456 participants. Among these, 745 were diagnosed with PMS, and 711 served as controls. The study aimed to elucidate the relationship between Vitamin D and Vitamin B6 supplementation and PMS. The analysis was conducted using continuous and dichotomous methods within fixed and random-effect models, depending on heterogeneity, to calculate odds ratios (OR) with 95% confidence intervals (CIs). **Results:** Vitamin B6 supplementation was significantly associated with reduced PMS scores compared to the control group (OR, -10.22; 95%CI, -15.49 to -4.95), suggesting a potential positive impact on adolescents' physical fitness and ability to participate in games and sports. However, Vitamin D levels did not show a significant correlation with PMS improvement (OR, -4.55; 95%CI, -9.70 to 0.60). **Conclusions:** The administration of Vitamin B6 has shown a significant improvement in PMS symptoms and scores in adolescents, potentially enhancing their physical activity and game participation. In contrast, Vitamin D did not demonstrate a significant effect on PMS. These findings underscore the potential role of Vitamin B6 in managing PMS symptoms in adolescents and its positive implications for their physical engagement and overall well-being.

KEYWORDS: Premenstrual syndrome; Vitamin D; Vitamin B6; PMS score

1. INTRODUCTION

physical, psychological, and behavioral symptoms that occur in the luteal phase of the menstrual cycle and significantly subside or disappear with the onset of menstruation. Affecting a substantial proportion of adolescent girls, PMS can profoundly impact their daily life, including their physical fitness and participation in games and sports activities(Verkaik, Kamperman, van Westrhenen, & Schulte, 2017). Recent research has been exploring the potential role of nutritional supplements in managing PMS symptoms. Among these, Vitamin D and Vitamin B6 are of particular interest. Vitamin D, known for its role in bone health and immune function, has been hypothesized to influence PMS due to its involvement in various hormonal pathways. On the other hand, Vitamin B6 is crucial for neurotransmitter synthesis and has been studied for its potential effects on mood and psychological PMS symptoms(Yonkers, O'Brien, & Eriksson, 2008).

The relationship between these vitamins and PMS symptoms in adolescents is especially pertinent given the developmental and lifestyle characteristics of this age group(Schiola, Lowin, Lindemann, Patel, & Endicott, 2011). Adolescence is a critical period for physical and psychological development, and the impact of PMS can extend beyond discomfort, potentially hindering participation in physical activities and sports - essential components of healthy adolescent development. Regular physical activity is known to improve mood, physical health, and overall quality of life, but the symptoms of PMS can act as a barrier to staying active(Verkaik et al., 2017).

Thus, this meta-analysis aims to evaluate the efficacy of Vitamin D and B6 supplementation in managing PMS symptoms in adolescent girls, with a focus on how these supplements might influence their physical fitness and willingness to participate in games and sports. Understanding the potential of these vitamins in alleviating PMS symptoms could offer new insights into non-pharmacological interventions for PMS management, promoting better health outcomes and quality of life for adolescents affected by this condition(AMICK, 2021).

2. Methods

According to the epidemiological declaration, a methodology was devised, which was then organized and analyzed in the form of a meta-analysis.

2.1 Study selection

The main goals of the current meta-analysis were to evaluate and assess the relationship between Vitamin D levels and vitamin B6 supplements

and premenstrual syndrome (PMS) compared with control from different previous clinical trials that were analyzed using statistical analysis tools such as frequency rate, odds ratio (OR), relative risk, or mean difference (MD) at a 95% confidence interval (CI). The criteria for inclusion of articles in the current meta-analysis were not constrained by the size of studies, while studies with no relationships, such as letters, and review articles, were eliminated from the study.

The meta-analysis model is depicted in Figure 1. The relationship between Vitamin D levels and vitamin B6 supplements and premenstrual syndrome (PMS) compared with control was compared to the control in the sensitivity analysis subcategory.

2.1.1 The criteria for inclusion of articles that were used in the current meta-analysis

1. Randomized controlled trials, Prospective, and retrospective clinical trials were all allowed to be incorporated into the current research. 2. Subjects included in studies should be PMS subjects. 3. Intervention programs assessment of Vitamin D and Vitamin B6 roles in PMS subjects versus control.

2.1.2 Studies exclusion criteria

1. Trials that do not evaluate or assess the relationship between Vitamin D levels and vitamin B6 supplements and premenstrual syndrome (PMS) compared with control. 2. Studies with messed parameters related to measured outcomes. 3. Studies that have no bearing on comparative results between PMS and control.

2.1.3 Identification

A systematic deep literature search was accomplished on MEDLINE/PubMed, Cochrane Library, OVID, Embase, and Google Scholar, and until the end of April 2022, using keywords such as; premenstrual syndrome; Vitamin D; Vitamin B6; serum levels; symptoms of PMS as shown in Table 1. P (population): PMS subjects; I (intervention/exposure) levels of Vitamin D or administration of Vitamin B6 in both PMS subjects and control; C (comparison): Vitamin D or Vitamin B6 in PMS subjects compared to controls; O (outcome): impact on PMS occurrence and score, S (study design): randomized clinical trials.

To eliminate duplicates, the research papers were grouped using EndNote software. Furthermore, all title and abstract data were subjected to a thorough review to eliminate any information that did not reflect any risk variables or the influence of the relationship between Vitamin D levels and vitamin B6 supplements and premenstrual syndrome (PMS) compared with

control.

Table 1: The strategy of Searching Scientific Databases

DATABASE	SEARCH STRATEGY
Pubmed	#1 "Premenstrual syndrome"[MeSH Terms] OR "Vitamin D "[MeSH Terms] OR "Vitamin B6" [All Fields] #2 "symptoms"[MeSH Terms] OR "serum level"[All Fields] #3 #1 AND #2
Embase	#1 ' Premenstrual syndrome '/exp OR Vitamin D'/exp OR Vitamin B6'/exp #2 'Symptoms/exp OR 'Serum level'/exp #3 #1 AND #2
Cochrane library	#1 (Premenstrual syndrome):ti,ab,kw OR (Vitamin D):ti,ab,kw OR (Vitamin B6):ti, ab, kw (Word variations have been searched) #2 (Symptoms):ti, ab, kw OR (Serum level):ti,ab,kw (Word variations have been searched) #3 #1 AND #2

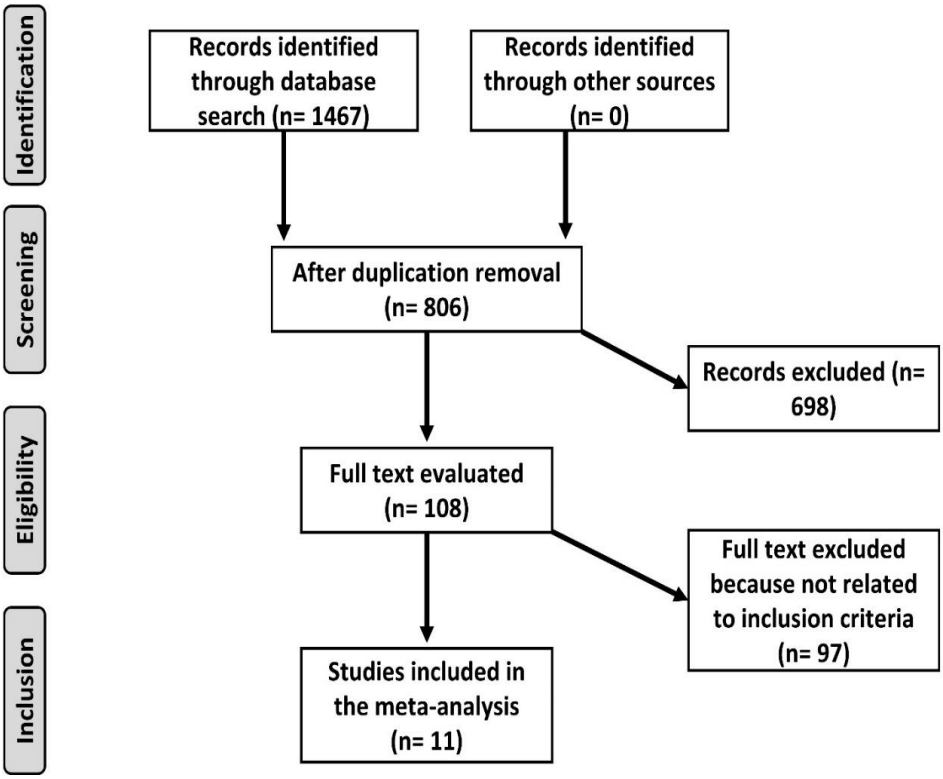

Figure 1: The mode of meta-analysis is depicted in this illustration diagram.

2.2 Screening

The subject-related and study-related data were entered into a standard format. Place of practice, the first author's surname, total subjects, country, year, primary outcome evaluation, treatment mode, duration of the study, categories,

statistical analysis, information source, and qualitative and quantitative evaluation were also included in a traditional form. Using the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1, the "Risk of Bias Tool" was used to evaluate the quality of the method.

2.2.1 Different levels related to bias risk might be found in the criteria for assessment.

Three levels of bias risks are identified in the evaluation of the criteria. When all quality parameters were satisfied, the bias was judged low risk; When parameters were not fulfilled or only partially completed, the risk was moderate; and the risk was high in cases where all of the quality criteria were not met or included. Examining the paper also reflected the presence of inconsistencies.

2.3 Statistical analysis

Using the random (I^2 =50% or more) and fixed (I^2 <50%) effect model, the odds ratio (OR) with a 95 % confidence interval (CI) was calculated using a continuous technique in the statistical analysis. Initially, the I^2 index ranged from 0% to 100%., while the heterogeneity scale ranged from 0 to 25 percent, 50 percent, and 75 percent, indicating no, low, moderate, and high heterogeneity, respectively. If I^2 was 50% or higher, the random effect was taken into account, and the fixed influence was considered if I^2 was less than 50%. Subgroup analysis was conducted to generate a statistically significant p-value of less than 0.05 from the first data set. The statistical analysis was carried out using two-tailed p values "Reviewer manager version 5.4.1" (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

3. Results

Among the 1467 unique reports, the current meta-analysis included 11 studies published between 1989 and 2017 that matched the inclusion criteria (Abbasi, Abbasi, Suhag, & Qureshi, 2017; Bertone-Johnson et al., 2014; Diegoli, Da Fonseca, Diegoli, & Pinotti, 1998; Doll, Brown, Thurston, & Vessey, 1989; Ebrahimi, Motlagh, Nemati, & Tavakoli, 2012; Kia, Amani, & Cheraghian, 2015; Maroofi, Rezaie, & Maroofi, 2003; Rajaei et al., 2016; Sharma, Kulshreshtha, Singh, & Bhagoliwal, 2007; Thys-Jacobs & Alvir, 1995; Thys-Jacobs, McMahon, & Bilezikian, 2007).

The current study included 1456 participants at the start of the study; 745 were PMS subjects, and 711 were controls as shown in Table 2. All studies evaluated the relationship between Vitamin D and Vitamin B6 and PMS for occurrence and PMS score compared with control. A total of 6 clinical trials compared the levels of Vitamin D for PMS subjects compared with control, while 5 studies assessed the relation between vitamin D deficiency and occurrence of PMS. While 5 trials evaluated the impact of Vitamin B6 supplements on PMS

scores. As proved in Figures 2-4, In comparison with the control group, the vitamin D levels were not significantly different from those compared with the control. While Vitamin B6 supplementation resulted in a significantly lower PMS score ((OR, -10.22; 95%CI, -15.49-4.95, p=0.0001, (I^2=93%)), Due to the high heterogeneity (I^2), a subgroup analysis was then performed to minimize heterogeneity among the included studies. Subgroup analysis was demonstrating the Vitamin D status on occurrence of PMS. The non-significant impact of vitamin D also was confirmed for dichotomous analysis (p=0.33) (OR, 1.16; 95 % CI, 0.86-1.55, ($I^2$0%)).

Because some of the included reports on these factors, ethnicity, and nutritional status, the pooled data did not consider them. Regarding study bias, we concluded that no study adequately covered all seven domains. There was a wide range in quality in the included studies' methods. Studies included in this analysis were of varying quality. Insufficient methodological tools were found in the randomized dressings-led trial.

Table 2: Characteristics of the included studies for the meta-analysis

STUDY	YEAR	COUNTRY	TOTAL	INTERVENTIONAL	CONTROL	VITAMINS
(AMICK, 2021)	2021	Iran	84	42	42	B6
(Sharma et al., 2007)	2007	India	40	20	20	B6
(Diegoli et al., 1998)	1998	Brazil	60	30	30	B6
(Maroofi et al., 2003)	2003	Iran	94	46	48	B6
(Doll et al., 1989)	1989	UK	32	16	16	B6
(Bertone-Johnson et al., 2014)	2014	USA	802	401	401	D
(Yonkers et al., 2008)	2008	Iran	59	31	28	D
(Thys-Jacobs et al., 2007)	2007	USA	115	68	47	D
(Thys-Jacobs & Alvir, 1995)	1995	USA	12	7	5	D
(Rajaei et al., 2016)	2016	Iran	73	41	32	D
(Abbasi et al., 2017)	2017	Iran	85	43	42	D
		Total	1456	745	711	

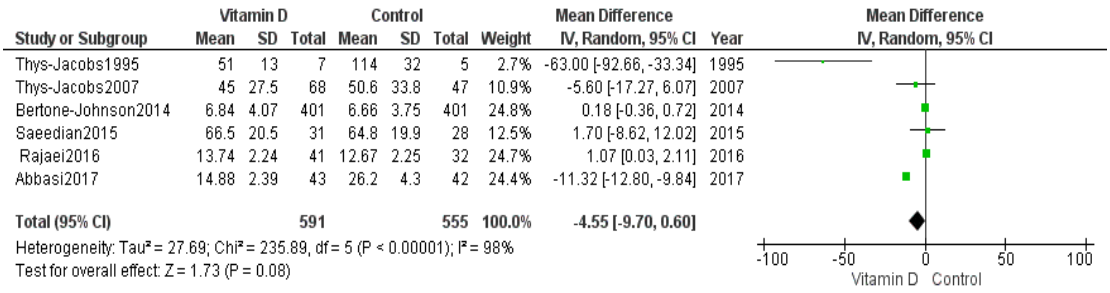

Figure 2: A forest plot illustrating the relationship between Vitamin D level and PMS compared with control.

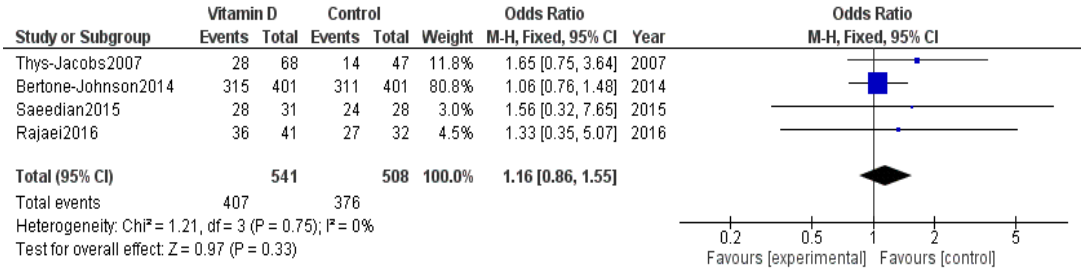

Figure 3: A forest plot illustrating the relationship between Vitamin D level and occurrence of PMS compared with control.

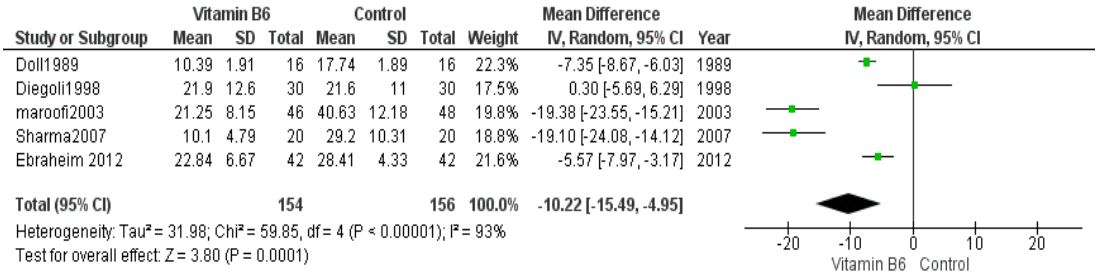

Figure 4: A forest plot illustrating the relationship between Vitamin B6 administration and placebo om PMS score.

4. Discussion

The current study involved a current meta-analysis that included 11 studies that included 1456 subjects at the start of the study; 745 were PMS subjects, and 711 were controls.(Abbasi et al., 2017; Bertone-Johnson et al., 2014; Diegoli et al., 1998; Doll et al., 1989; Ebrahimi et al., 2012; Kia et al., 2015; Maroofi et al., 2003; Rajaei et al., 2016; Sharma et al., 2007; Thys-Jacobs & Alvir, 1995; Thys-Jacobs et al., 2007) A total of 6 clinical trials compared the levels of Vitamin D for PMS subjects compared with control, while 5 studies assessed the relation between vitamin D deficiency and occurrence of PMS. While 5 trials evaluated the impact of Vitamin B6 supplements on PMS scores. Though, because some of the included trials have a small sample size (only 3 studies had a size of sample less than 50 PMS subjects), careful analysis of the results is required, implying the necessity for further trials to confirm the

current findings or possibly to have a substantial effect on the assessment of the intervention impact. In addition, the high heterogeneity among the involved studies raised the need for subgroup analysis. When compared to control groups, there were significant reductions in PMS mean scores after therapy with vitamin B6. Furthermore, after the treatment, the two groups' mean PMS scores were significantly different. The primary goal of the current study was to evaluate to assess the relationship between Vitamin D levels and vitamin B6 supplements and premenstrual syndrome (PMS) compared with control. Through this analysis, it was discovered that there is no link between serum 25(OH)D and PMS, which contradicts the findings of all previous interventional research. Some points should be emphasized in the case of clinical studies, which have all found significant links between vitamin D and PMS. An extremely high dose of vitamin D (50000 IU/week) was given in one trial (Bahrami et al., 2018), which is solely advised for the treatment of vitamin D deficiency (Holick et al., 2012). Furthermore, because there was no control group in this trial, comparing the effect of vitamin D supplementation to the placebo effect on PMS severity is impossible. Another two studies looked at the effect of calcium and vitamin D on PMS and found that calcium can help relieve some PMS symptoms (Thys-Jacobs, 2000); however, it's difficult to draw clear conclusions about the effect of vitamin D alone from these research. Furthermore, only one study in clinical trials was rated as high-quality, which should be taken into account when interpreting the results (Gatmaitan, Werner-Gibbings, Donati, Saha, & Black, 2020).

The present study also found that taking a placebo helped with PMS symptoms. This reduction was noticeably smaller than that seen in the intervention group, but it still suggests that a placebo may have some beneficial effects. There have been many scientific and clinical researches on premenstrual syndrome, all of which have found that symptom decrease occurs in the control groups (with or without the use of a placebo). It appears that receiving attention can improve participants' mental health and make it easier to cure the premenstrual syndrome. Previous studies on the optimal vitamin B6 dose have yielded conflicting findings. However, some studies found no significant impact on PMS symptoms even with large doses of vitamin B6 and stressed the requirement for high doses of vitamin B6 over a lengthy time (through the entire menstrual cycle). Some studies have found that even low doses of vitamin B6 are ineffective. Symptoms of PMS were dramatically reduced in a two-month trial of Iranian women who took 250 mg of vitamin B6 daily, compared to the women who took a placebo. After comparing vitamin B6 with placebo in India, Sharma et al.(Sharma et al., 2007) found that taking 100 mg of vitamin B6 daily for three months dramatically reduced PMS symptoms. Doll et al.(Doll et al., 1989) highlighted the positive effects of taking 100 mg of vitamin B6 every day for three months in the United States. Wyatt et al. (Wyatt, Dimmock, Jones, & O'Brien, 1999) conducted a meta-analysis that found the benefits to be real. Nonetheless, the current meta-analysis found that different

doses of vitamin B6 had similar effects. Vitamin B6's safety and efficacy have not been established. This may be because vitamin B6 was used at such a low dose in the majority of studies included in this meta-analysis. Finally, the findings of the current meta-analysis showed a statistically significant relation between Vitamin B6 and reduced PMS score and there was no significant impact on vitamin D levels for both intervention and control groups regarding the occurrence of PMS.

5. Limitations

One of the study's drawbacks was that there were many biases because numerous papers were eliminated from the current meta-analysis because they did not match the inclusion criteria. Furthermore, there was some skepticism about how to link criteria like ethnicity, and nutritional status to this study. The current study looked at the potential to evaluate the relationship between Vitamin D levels and vitamin B6 supplements and premenstrual syndrome (PMS) compared with control. Using data from prior studies, the analysis may be skewed because of missing information. The meta-analysis included 11 studies, three of which were small (under 50 participants). Influence bias could result from a collection of lost data and unpublished studies. Subjects' weight was variable among the different studies.

6. Conclusions

The findings of this meta-analysis highlight the significant role of Vitamin B6 supplementation in alleviating symptoms of premenstrual syndrome (PMS) in adolescent girls. This improvement in PMS symptoms can potentially enhance physical fitness and encourage active participation in games and sports, crucial aspects of adolescent health and development. Vitamin B6's efficacy in reducing PMS scores points towards a promising, non-invasive treatment option that could positively impact the quality of life and physical activity levels in this demographic. Conversely, our analysis did not find a significant correlation between Vitamin D levels and the improvement of PMS symptoms. This suggests that while Vitamin D is essential for overall health, its direct role in managing PMS symptoms, particularly in relation to physical activity and sports participation, may be limited.

These results emphasize the importance of targeted nutritional interventions in managing health conditions like PMS, which can significantly affect the daily lives of adolescents. Healthcare providers and caregivers should consider the potential benefits of Vitamin B6 supplementation as part of a holistic approach to managing PMS, thereby supporting the physical and psychological well-being of adolescents. Further research is encouraged to explore the long-term effects of these supplements and their specific impact on physical activity and sports engagement in this population.

Declarations

a) Ethical approvals and consent of participation: Not applicable

b) Conflicts of interests: None

c) Consent for publication: Not applicable

d) Funding: Not applicable

e) Acknowledgment: No

Availability of data and materials

The corresponding author is bound to give the database of meta-analysis on request.

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