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The Effect of Calcium on Premenstrual Syndrome: A Meta-Analysis Study

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Abstract

Aims. This study systematically reviewed the available randomised controlled trials to elucidate the general relationship between calcium and PMS.

Material and Methods. Meta-analysis followed PRISMA guidelines using the PICOS format, considering CONSORT recommendations. Searches were performed in PubMed, Web of Science, Google Scholar, and Scopus databases between 02.11.2022- 02.12.2022 using the keywords "premenstrual syndrome and calcium" and "premenstrual tension and calcium" and "premenstrual dysphoric disorder and calcium". The search strategy was applied to articles published between January 2012 and December 2022. The Cochrane tool was used to assess the risk of bias in RCTs. Fixed-effect models and random-effect models were used for meta-analysis based on heterogeneity. Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines were followed in our study.

Results. This systematic review and meta-analysis included six randomised controlled trials published between 2013 and 2020. According to the pooled results of the six studies, calcium reduced the severity of PMS complaints (p=0.002; I2 = 76.2%) when calcium administration was compared with the control group for the reduction of PMS complaints. On the other hand, the severity of PMS complaints did not change when calcium administration for the reduction of PMS complaints was compared with other treatments (p=0.416; I2 = 54.7%).

Conclusions. This study showed that calcium effectively reduced the severity of PMS complaints compared to the control groups. In contrast, the severity of PMS complaints did not change when other treatments and calcium administration were compared.

Keywords: PMS, calcium, randomized controlled, meta-analysis.

Introduction

Premenstrual syndrome (PMS) is a common condition that affects the health of millions of women of reproductive age worldwide [1]. PMS is characterised by clinically significant psychological and physical symptoms. PMS, which occurs during the luteal phase of the menstrual cycle, ends with the onset of menstrual bleeding [2–5]. PMS is defined as a clinical condition characterised by emotional and physical symptoms that begin on the 5th day before the menstrual period and end around the 4th day after the menstrual period, and is not associated with any physiological disease [6].

Although PMS is thought to occur as a result of hormonal changes that accompany ovulation, the cause is not known for certain [7]. The hormone progesterone plays an important role in the mechanism of PMS. Progesterone metabolites bind to the gamma-aminobutyric acid (GABA) receptor in the brain, changing the structure of the GABA receptor and reducing its sensitivity. As a result, serotonin levels decrease and PMS symptoms occur [7]. Premenstrual symptoms have a significant impact on women's quality of life, increasing healthcare utilisation and reducing work productivity [8]. Among women of reproductive age, 47.8% experience PMS symptoms [5]. Twenty per cent of these women experience

symptoms so severe that they are unable to carry out their daily work, and the remainder experience mild to moderate symptoms. The clinical symptoms of PMS can be divided into two groups: psychological and somatic. While psychological symptoms include social isolation, aggression, fatigue, suicidal thoughts, irritability and depression, somatic symptoms include oedema, weight gain/loss, stiff/low back and headaches, breast tenderness, swelling, changes in diet and oedema [2–9]. Pharmacological and non-pharmacological treatments are used to reduce PMS symptoms. Non-pharmacological treatments are used to treat mild symptoms, while pharmacological treatments, serotonin reuptake inhibitors (SSRIs), are used to treat severe symptoms [8].

Non-pharmacological treatments are called complementary therapies and are safer and have fewer complications than pharmaceutical methods [10]. Examples of these treatments include aerobic exercise, cognitive behavioural relaxation therapy, magnesium/vitamin B6/D or L-tryptophan supplementation, or complex carbohydrate intake [11]. The literature highlights the relationship between fluctuations in calcium levels and PMS symptoms. It is known that serum calcium levels are reduced prior to the menstrual period, are lower in the luteal phase of the menstrual cycle than in the follicular phase, and this low level can exacerbate PMS symptoms by causing hallucinations, depression and restlessness [12–14]. Several studies have shown that calcium may be beneficial in alleviating psychotic disorders associated with PMS. Some interventional studies have shown that calcium supplementation is associated with a reduction in the incidence of various symptoms of PMS [15,16], and there are also studies in the literature suggesting that there is no association [17, 18].

It can be seen that there are conflicting results in the literature regarding the studies that have investigated the relationship between the severity of PMS symptoms and calcium supplementation. This trial was conducted to assess the effectiveness of calcium supplementation on the severity of PMS symptoms.

Methods

Research Strategy

This is a systematic review and meta-analysis. The reporting of the manuscript and the preparation of the study protocol were carried out in accordance with the PRISMA statement - checklist for reporting elements in systematic reviews and meta-analysis. The protocol of this study was registered in the PROSPERO database (CRD42022372284). There were no ethics applications, conflicts of interest or funding to report for the conduct of the systematic review and meta-analysis. To minimise the risk of bias in this study, the literature search, selection of articles, data extraction and quality assessment of the articles were carried out separately by two researchers. In case of disagreements and inconsistencies in selection, the opinion of the other researcher was sought and disagreements were resolved through discussion. In addition, in order to complete all stages of the study, all researchers attended a course on systematic review and meta-analysis, in which pilot application and screening stages were carried out on a topic not included in this study.

Selection of Studies

The identification and selection process of the studies to be included in this study was carried out independently by two researchers. The researchers identified the studies based on the inclusion criteria. The researchers analysed the included studies and the repetitive studies were excluded from this study. All included studies were analysed according to title, abstract and full text content. In case of disagreements about the existing studies, all researchers discussed the issue in a session and reached a consensus. PRISMA Flow Diagram Figure 1 shows the selection process of the studies.

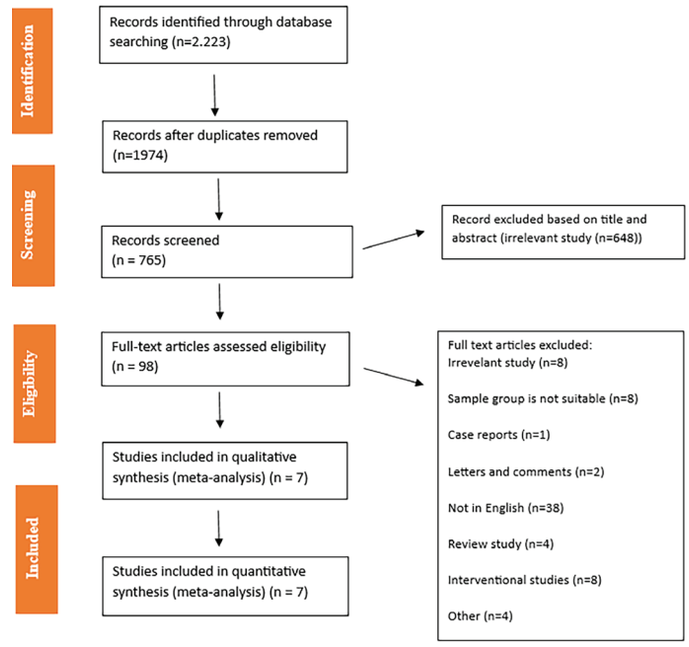

Figure 1 – PRISMA Flow Diagram

Google Scholar, Web of Science, Pubmed and Scopus databases were searched by the researchers between October and December 2022 to conduct this systematic review and meta- analysis study. The keywords "premenstrual syndrome and calcium" and "premenstrual tension and calcium" and "premenstrual dysphoric disorder and calcium" were used to search the databases.

PICOS identified for this study:

Population: Women with Premenstrual Syndrome

Intervention: Calcium and other interventions

Comparison: Placebo

Outcomes: Severity of Premenstrual Symptoms

Study design: Randomised Controlled Trials published in English.

Inclusion criteria;

- Studies published between 2012-2022,
- Randomised Controlled Trials examining the effect of calcium on PMS
- Studies published in English,

Exclusion criteria;

- Studies such as letters to the editor, case reports, papers that are not published as full articles
- Studies whose full text could not be accessed.

Data Extraction

In this review, the researchers used a data extraction tool to obtain the research data. This data extraction tool was used to obtain data about the studies included in the systematic review and meta-analysis, such as where and when the studies were conducted, method, sample size and measurement tool used. Data extraction was performed independently by two authors under the supervision of the third and fourth authors.

All retrieved articles underwent a review process. Duplicate articles were initially excluded. The titles and abstracts of the

remaining studies were read in detail to determine whether they were relevant to this study. The full text of the scanned abstracts and titles was then accessed and carefully reviewed against the inclusion criteria. As a result of the above steps, the articles that met the inclusion criteria were used in the analysis of this study.

Study Quality Assessment

In this review, two authors independently assessed the risk of bias of the studies included in the analysis. The other author performed the review. Disagreements were resolved by discussion between the researchers. The quality of the included trials was assessed using the JBI Critical Appraisal Checklist for Randomised Controlled Trials published by the Joanna Briggs Institute. This checklist consists of 13 items and includes no, yes, not applicable and uncertain responses. In the checklist, items with 'no' and 'unclear' answers received 0 points, while items with 'yes' answers received 1 point. All included studies were analysed, including their titles and abstracts. The full texts of the studies were then examined in the checklist assessment. The scores of the studies are shown in Table 1.

Table 1 JBI Critical Appraisal Checklist For Randomized Controlled Trials Assessment

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	Total*
Bharati, 2016	1	0	1	1	0	0	1	1	1	1	1	1	1	**10**
Samieipour, Elahe et al., 2016	1	1	1	1	0	0	1	1	1	1	1	1	1	**11**
Shobeiri et al., 2017	1	1	1	1	1	0	1	1	1	1	1	1	1	12
Yonkers et al., 2013	1	1	1	1	1	0	1	1	1	1	1	1	1	**12**
Yurt et al., 2020	1	1	1	0	0	0	1	1	1	1	1	1	1	**10**
Mandana& Azar, 2014	1	1	1	0	0	0	1	1	1	1	1	1	1	10

*The numbers shown in the columns (1 to 13) are the evaluation items given in the JBI Critical Appraisal Checklist For Randomised Controlled Trials Assessment.

Evaluating the potential of bias

The selected studies underwent risk of bias evaluation in order to produce a quantitative overview of the therapeutic effects of calcium consumption on PMS. Risk of bias was evaluated using the Cochrane risk of bias method for randomized trials (RevMan 5.2.0). Two evaluators worked separately to finalize the assessment after reading the original articles. The final evaluation results were chosen following a discussion about whether the assessors' scores differed.

Statistical Analysis

Data from the trials were coded and analysed using the Comprehensive Meta-Analysis free trial statistical software package (https://www.meta-analysis.com/pages/demo.php). Heterogeneity between studies was assessed using Cochran Q and Higgins I^2 tests, and an $I^{2'}$ ratio greater than 50% was considered an important indicator of heterogeneity. Random-effects results were considered when $I^{2'}$ was greater than 50%, and fixed-effects results were considered when the value was lower. For each outcome variable, the 95% confidence interval (CI) was calculated and estimated values were calculated. All tests were calculated as two-tailed. Results were considered statistically significant if the p-value was less than 0.05.

Results

Screening Results

The first stage of the search identified 2223 trials. After eliminating repetitive studies, a selection was made by evaluating the abstracts and titles of the studies. In terms of suitability for our meta-analysis, 117 studies were identified as candidates for inclusion and the full texts of these studies were accessed. The full texts of the studies were analysed. In this study, calcium (n): 187; control (n): 184 sample size and 6 published (Table 2).

Effects of Calcium on Premenstrual Syndrome

In this meta-analysis, calcium-treated experimental groups were compared with non-treated control groups. The standardised difference value of calcium against the control group was calculated as -0.768 (95% CI: -1.255 to -0.281). When calcium administration for the reduction of PMS complaints was compared with the control group, it was determined that calcium reduced the severity of PMS complaints (p=0.002; I2 = 76.2%) (Figure 2). No publication bias was found (Figure 3).

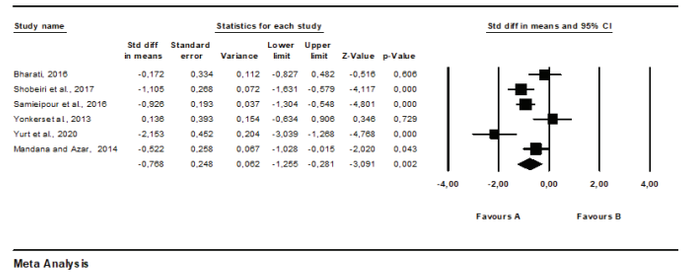

Figure 2 – Forrest graph showing the changes in the severity of PMS complaints between the calcium-administered experimental group and the non-administered control group.

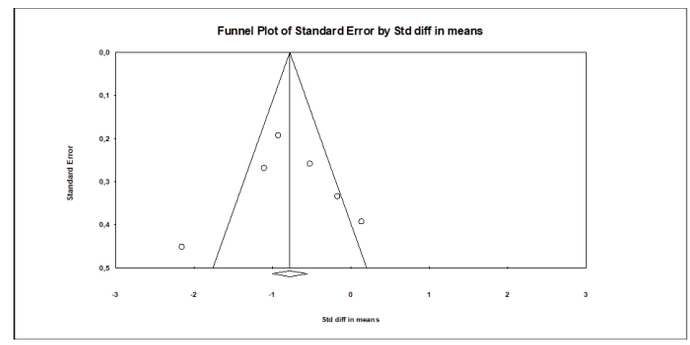

Figure 3 – Bias risk assessment of regarding changes in the severity of PMS complaints between the experimental group given calcium and the control group without calcium

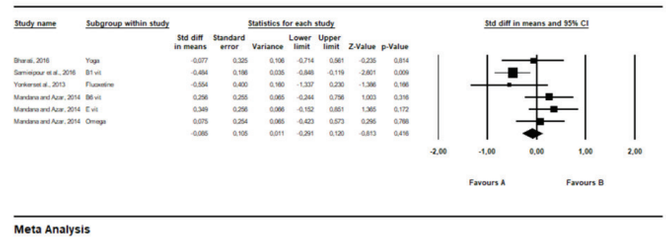

Figure 4 – Forrest graph showing the changes in the severity of PMS complaints between calcium administration and other administrations.

Table 2 Summary of the basics of studies included in the meta-analysis based on the PRISMA method

Author, Year	n	Country	Participants	Intervention group	Control goup	Outcomes	Instrument	Results
Bharati, 2016	65	India	Young female medical students	Yoga group (5 days a week, 1 hour a day, for three months) Calcium carbonate tablet group (500 mg, for three months)	No intervention	Severity of PMS complaints	Questionnaire prepared by researchers	Both interventions reduced PMS symptoms, suggesting that yoga was more effective than calcium supplementation in relieving PMS symptoms.
Samieipour, Elahe et al., 2016	264	Iranian	Students staying in dormitories of Ilam Medical Sciences University	B1 group (100 mg tablet daily, for 2 cycles) Calcium carbonate (500 mg tablet, for 2 cycles) B1+Calcium carbonate (tablet containing 100 mg vitamin B1 + 500 mg calcium carbonate)	Placebo (1gr food starch tablet daily)	Severity of PMS complaints	PMS diagnosis questionnaire	Mean reduction in PMS symptoms in groups Vitamin B1 calcium >Calcium >Vitamin B1>Placebo
Shobeiri et al., 2017	66	Iranian	Female students of Hamadan University of Medical Sciences diagnosed with PMS in 2014	Calcium (500 mg daily, for two months)	Placebo (500 mg starch tablet daily)	Severity of PMS complaints	Daily Record of Severity of Problems scale	A daily intake of 500 mg of calcium is effective in reducing PMS symptoms.
Yonkers et al., 2013	39	USA	Women who meet the inclusion criteria applying for private gynecological examinations in the USA	Fluoxetine group (10 mg twice daily, for four cycles); Calcium carbonate group (600 mg twice daily, for four cycles)	Placebo (placebo tablets that look similar to calcium and fluoxetine tablets)	Severity of PMS complaints	The Inventory of Depressive Symptomatology, Premenstrual Tension Scale, Clinical Global Impression Severity and Improvement scales, and Daily Record of Severity of Problems	Fluoxetine is more effective at reducing premenstrual syndrome symptom severity than calcium.
Yurt et al., 2020	31	Turkish Republıc of Northern Cyprus	The sample consists of voluntary students studying at the Eastern Mediterranean University who meet the study inclusion criteria.	Intervention group (cheddar cheese made from cow's milk (50 g), at least 400 ml of milk and 150 g of yoghurt every day)	No intervention	Severity of PMS complaints	Premenstrual Syndrome Scale (PMSS), the short form of the Quality of Life Scale (SF-36).	Intervention group effective in reducing the severity of PMS
Mandana & Azar, 2014	200	Iranian	All female students of Islamic Azad University Sari branch	Calcium group (1 g calcium per day, for three cycles), Vit E group (100 mg Vit E tablet daily, for three cycles) Omega 3 (1 g capsule fish oil daily, for three cycles), Vit B6 group (40 mg Vit B6 daily, for three cycles)	Placebo (starch tablet)	Severity of PMS complaints	Rosignol Bonlender questionnaire	Vit E, Vit B6, calcium and omega-3 are effective in reducing the severity of PMS

When calcium was compared with some other interventions in the evaluation of the severity of PMS complaints, the standardised difference value was calculated as -0.085 (95% CI: -0.291 to 0.120). The severity of PMS complaints was found to be unchanged when calcium administration was compared with other treatments to reduce PMS complaints (p=0.416; I2 = 54.7% (Figure 4). No publication bias was found (Figure 5).

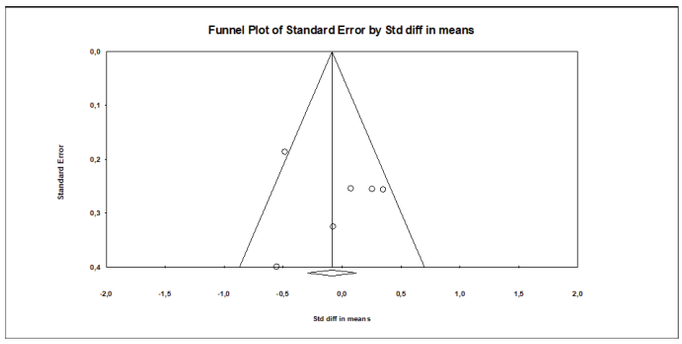

Figure 5 – Bias risk assessment of regarding changes in the severity of PMS complaints between calcium application and other applications.

Discussion

This study is a systematic review and meta-analysis of the effects of calcium on premenstrual symptoms. It included 6 randomised controlled trials that were conducted between 2012 and 2022. There were two main findings from this systematic review and meta-analysis. Calcium was found to reduce the severity of PMS symptoms (p=0.002; I2 = 76.2%) (Figure 2). It was also found that there was no change in the severity of PMS symptoms when calcium was compared with other treatments in reducing the severity of PMS symptoms (p=0.416; I2 = 54.7%) (Figure 4).

The prevalence of PMS was found to be 43%, 52.2%, 53% and 70.8% in systematic reviews and meta-analysis conducted in India, Turkey, Ethiopia and Iran [19–22]. While the prevalence of PMS varies between 19-30% in the USA, it has been reported to be 12% in France and 10% in Switzerland [23, 24]. In a worldwide meta-analysis study by Moghadam et al, the prevalence of PMS was 47.8% [23]. Women who have 12 menstrual cycles per year spend almost 3 months with premenstrual symptoms. This situation reduces women's quality of life and negatively affects their health [25].

Although individualised treatments for PMS symptoms are recommended, PMS symptoms can be treated with non-pharmacological methods (lifestyle changes, cognitive behavioural therapy, dietary supplements), pharmacological methods (chamomile, combined oral contraceptives, serotonin reuptake inhibitors, other psychotropic agents, gonadotropin-releasing hormone analogues) and surgical treatment options [24].

When looking at systematic reviews and meta-analysis studies of treatment options, treatments such as exercise [26, 2], aerobics [27], reflexology [28], yoga [29], aromatherapy [30], chaste herb [31], traditional Chinese medicine [32], dietary supplements and herbal medicines [33], and vitamin D [34] have been found to be effective in reducing PMS symptoms.

Abdi et al investigated the effects of vitamin D and calcium on PMS symptoms and found that calcium and vitamin D supplements could eliminate or reduce PMS symptoms [35]. The study by Arab et al, which investigated the beneficial role of calcium in PMS symptoms, found that calcium may be effective in reducing the incidence of PMS and PMS-related symptoms. [34]. Several studies have shown that women with PMS have low serum calcium levels and that serum calcium levels may reduce the incidence of PMS-related symptoms [36–39]. In a randomised controlled trial conducted by Mandana and Azar, calcium was found to be effective in reducing PMS symptoms [40]. The study by Kermani et al found that PMS symptoms in women who took a combination of calcium and vitamin E decreased and in some cases disappeared [41]. Some studies suggest that vitamin D and high calcium intake may be effective in reducing PMS-related symptoms, including osteoporosis and some cancer risks. Calcium and vitamin D supplementation appears to be an inexpensive, accessible, low-risk and acceptable approach to reducing or eliminating PMS symptoms [42, 34]. ACOG recommends 1.2 mg of calcium supplementation daily to reduce both the physical and psychological symptoms of PMS and to reduce water retention and breast tenderness [31, 43, 44]. In the meta-analysis, calcium supplementation was found to be effective in reducing PMS symptoms. In terms of these results, our study shows similar results to the literature.

In our study, the use of calcium was compared with other applications in reducing PMS symptoms and it was observed that the severity of PMS symptoms did not change with calcium application. In the study by Yonkers et al. comparing fluosectin, calcium and plasebo in the treatment of PMS symptoms, fluosectin was found to be beneficial, whereas the effect of calcium was much less [18]. In a study by Bharati comparing the effects of yoga and oral calcium supplementation in reducing PMS symptoms, it was found that yoga and calcium supplementation were effective in reducing PMS symptoms, but yoga was more effective than calcium supplementation [45].

Conclusion

According to the results of this study, calcium was found to be effective in reducing the severity of PMS symptoms when calcium supplementation was compared with control groups. The use of calcium supplements by women to reduce the severity of PMS symptoms is considered a simple and effective method. In addition, when other treatments for PMS symptoms were compared with calcium, there was no change in the severity of PMS symptoms. More research is needed to compare the effectiveness of other treatments and calcium supplements.

Relevance for clinical practice

Our study shows that calcium supplementation can be recommended as a safe, effective and convenient method to improve patients' quality of life. Nurses working in clinics should consider calcium supplements in their care for individuals experiencing PMS symptoms and inform individuals about calcium supplements.

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