

## Beneficial Role of Calcium in Premenstrual Syndrome: A Systematic Review of Current Literature

### Abstract

Since premenstrual syndrome (PMS) is one of the most common and debilitating disorders in women, risk factor modification is an urgent health priority. Therefore, this systematic review aimed to summarize and discuss the outcomes of observational and interventional studies in humans regarding the relationship between Calcium and PMS. PubMed, Scopus, ISI web of sciences and Google scholar were searched up to January 2019 to identify relevant studies. The Newcastle-Ottawa and Jadad scales were used for quality assessment. A total of 14 studies (8 interventional and 6 observational) met our inclusion criteria. Majority of the studies showed that not only serum calcium levels are lower in PMS subjects, but also calcium supplementation could significantly improve the incidence of PMS and its related symptoms. This systematic review suggests a beneficial role for calcium in PMS subjects. However, in order to draw a firm link between calcium and PMS, further dose-response clinical trials with larger sample size and better methodological design are warranted.

**Keywords:** Calcium, premenstrual syndrome, systematic review

### Introduction

Women's health is one of the main goals of social and economic development of societies; therefore, problems and diseases compromising women's physical and mental health, such as premenstrual syndrome (PMS), are among health priorities.<sup>[1]</sup> PMS is characterized with a set of physical and emotional symptoms, including mood swings, tender breasts, food craving, fatigue, irritability, and depression beginning in the luteal phase of the menstrual cycle and resolving with the start of menstruation.<sup>[2]</sup> A recent meta-analysis estimated a worldwide prevalence of 10%–98%.<sup>[3]</sup> The syndrome is associated with significant economic burden. Distress and impairment in interpersonal or workplace functioning occur in a regular basis every month which can lead to significant amount of absenteeism at work and increase in medical costs.<sup>[4]</sup> Therefore, sufficient attention is needed to decrease its undesirable effects.

The etiology of PMS appears to be related to ovarian function, as suppression of ovarian hormone secretion markedly attenuates PMS,<sup>[5]</sup> although differences in ovarian steroid hormones have not

been consistently observed between symptomatic and asymptomatic women. Several biological, social, and behavioral factors have consistently been positively associated with PMS, whereas demographic factors, education, employment, and marital status have shown inconsistent relationships.<sup>[6]</sup> Younger age, less education, and higher levels of perceived stress have been reported to be risk factors for premenstrual emotional symptoms.<sup>[7,8]</sup>

Among various pharmacological treatments recommended for women with PMS, selective serotonin reuptake inhibitors (SSRIs) have been evaluated as the first-line of therapy.<sup>[9]</sup> These therapies may be effective at resolving PMS in many women, but they are also associated with significant side effects and can be expensive. Alternatives to hormone therapy, such as dietary supplementation, are being evaluated.<sup>[10]</sup> Non-pharmacologic management with some evidence for efficacy includes cognitive-behavioral relaxation therapy, aerobic exercise, as well as magnesium, vitamin B6/D, or L-tryptophan supplementation or intake of complex carbohydrates.<sup>[11]</sup>

Also, scientific evidence suggests that cyclic fluctuations in calcium levels may help to explain some features of PMS. Changes in

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extracellular calcium concentration could have stimulatory effects on neuromuscular junctions,<sup>[12]</sup> and irritability, mania and agitation have been reported in conjunction with hypocalcemia.<sup>[13]</sup> Calcium supplementation may act by resolving an underlying physiologic deficit, suppressing parathyroid hormone secretion, and, ultimately, reducing neuromuscular irritability and vascular reactivity.<sup>[13]</sup> The possibility that calcium can be useful in alleviating mood disorders associated with PMS has been evaluated in various studies. Several interventional studies found that calcium supplementation was associated with reductions in the incidence of several symptoms of PMS.<sup>[5,11,13]</sup> Also, there is cross-sectional evidence indicating an evident association between PMS symptoms and calcium status.<sup>[14-16]</sup> However, the results were inconsistent and several studies found no such an association.<sup>[17,18]</sup> To address the divergence mentioned above, we carried out this systematic review on the observational and interventional studies to explore the association between calcium and PMS in general populations to reach a firm conclusion in this regard.

## Methods

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement and registered on Prospero database (CRD42018114474).<sup>[19]</sup>

### Data source and search strategy

We searched relevant databases including PubMed, Scopus, ISI web of sciences and Google scholar up to January 2020 to identify relevant studies. Furthermore, the reference lists of the eligible papers were also reviewed to discover additional relevant studies. The following search strategy was run in PubMed and tailored to each database when necessary: “calcium” [Title/Abstract] OR “Ca” [Title/Abstract] AND “premenstrual syndrome” [Title/Abstract] OR “premenstrual dysphoric disorder” [Title/Abstract] AND “premenstrual tension” [Title/Abstract] OR “PMS” [Title/Abstract].

### Inclusion criteria

Articles were considered for inclusion if they assessed the association between serum Ca level or Ca supplementation and prevalence of PMS or its related symptoms. Studies assessing calcium effect in combination with other elements including vitamin D or the consumption of dairy products as a source of calcium were excluded. Non-human studies, review articles, case reports, editorials and poster abstracts were excluded as well.

### Data extraction

Pairs of independent reviewers screened the titles and abstracts of each study prior to full-text screening of nominee studies. Any divergences in terms of the decision on a given study were dealt with via discussion and if necessary, arbitration by a third reviewer. For all included studies, two

reviewers independently extracted information, including first author’s name, year of publication, location of the study, sample size, participants’ age, study design, dietary and PMS assessment method and statistical adjustment.

### Study quality

The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to assess the quality of each study.<sup>[20]</sup> Studies with 7–10, 5–6 and 0–4 points were identified as high, moderate, and low quality, respectively.<sup>[21]</sup>

Jadad scale for reporting randomized clinical trial (RCT) was used to assess the quality of interventional studies. In this scale, studies with 3 points or more were ranked as high quality.<sup>[22]</sup>

## Results

### Search results

Our initial search through databases identified 361 papers. After removing duplicates, the remaining 134 articles were reviewed based on the title and abstract by two independent reviewers. Totally, 79 articles were retrieved and reviewed based on full-text availability, and finally, 13 studies met our inclusion criteria and were included in our systematic review. The PRISMA flow diagram summarizes the results of study selection process for this systematic review [Figure 1].

### Overview of the included studies

Studies included in this systematic review were carried out between 1989 and 2019. In total, 1185 and 1460

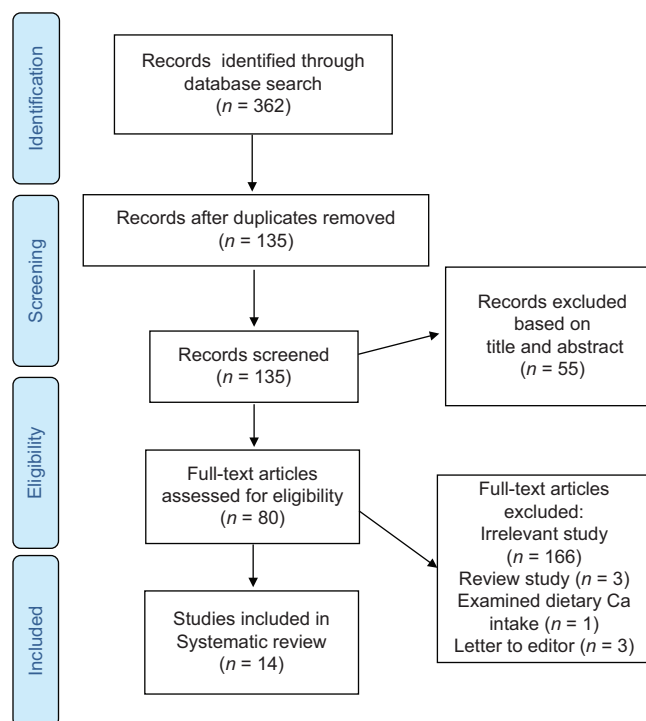


Figure 1: The flow diagram of study selection

participants were recruited in the interventional and observational studies, respectively. Among 14 studies included, 8 (7 RCTs<sup>[18,23-28]</sup> and 1 quasi-experimental<sup>[29]</sup>) were interventional and 5 (3 case-controls<sup>[14-16]</sup> and 3 cross-sectional<sup>[17,30,31]</sup>) were observational. In terms of study location, 7 papers were conducted in Iran,<sup>[14,17,23-26,31]</sup> 6 in United States<sup>[15,16,18,27,28,30]</sup> and one in India.<sup>[29]</sup> Only 3 articles mentioned the dietary assessment method.<sup>[14,27,30]</sup> The dose of calcium administered in interventional studies, mainly in the form of calcium carbonate, ranged from 500 to 1200 mg daily. Based on the quality assessment scales, 5 interventions<sup>[18,25-28]</sup> and 1 observational<sup>[17]</sup> study ranked as high quality. Characteristics of the included studies are illustrated in Tables 1 and 2.

### Interventional studies

The efficacy of calcium supplementation in patients with PMS was examined in 7 randomized clinical trials<sup>[18,23-27]</sup> and 1 quasi-experimental study.<sup>[29]</sup>

In the earliest study found, Jacobs *et al.* explored the efficacy of calcium supplementation in thirty-three women with premenstrual syndrome (PMS). Each participant received six months of treatment involving three months of daily calcium supplementation (1,000 mg of calcium carbonate) and three months of placebo. Results demonstrated a reduction in symptoms on calcium treatment during both the luteal and the menstrual phases of the reproductive cycle. Calcium supplementation had no effect during the inter-menstrual phase. 73% of the women reported fewer symptoms during the treatment phase on calcium, 15% preferred placebo, and 12% had no clear preference. Three premenstrual factors (negative affect, water retention, and pain) and one menstrual factor (pain) were significantly alleviated by calcium.<sup>[27]</sup>

A few years later in 1998, same authors evaluated the effects of Ca carbonate on the luteal and menstrual phases of the menstrual cycle among 466 healthy, premenopausal women with PMS (32.8 ± 6.7 years old). Subjects were randomly assigned to receive 1200 mg of elemental Ca per day in the form of calcium carbonate or placebo for 3 menstrual cycles. During the luteal phase of the treatment cycle, a significantly lower mean symptom complex score was observed in the Ca-treated group for both the second and third treatment cycles ( $P < 0.05$ ). By the third treatment cycle Ca effectively resulted in an overall 48% reduction in total symptom scores from baseline compared with a 30% reduction in placebo. All 4 symptom factors (negative affect, water retention, food cravings, and pain) were significantly reduced by the third treatment cycle.<sup>[27]</sup>

Moreover, the efficacy of Ca supplementation in young female college students suffering from PMS was similarly examined in another double-blind clinical trial in 2009. The subjects (179 women; mean age 21.4 ± 3.6 years old) were divided in two groups; one group received placebo and the other received 500 mg of Ca carbonate twice daily

for 3 months. Results showed that calcium supplements reduced early fatigability, changes in appetite, and depression in women with PMS ( $P < 0.05$ ).<sup>[23]</sup>

Next study was performed in 2016 aiming to attenuate symptoms of PMS by simple lifestyle measures like yoga and/or oral Ca among fifty-eight subjects (18-22 age range) diagnosed with PMS. Twenty girls were given yoga training (45 minutes daily, five days a week, for three months). Another group of 20 was given oral tablets of Ca carbonate daily (500 mg, for three months) and rest 18 girl served as control group. The yoga and Ca groups showed a significant decrease ( $P < 0.05$ ) in number and severity of premenstrual symptoms whereas in the control group there was not the significant difference.<sup>[29]</sup>

In another attempt, in 2016, Samiepour *et al.* investigated the effects of Ca and vitamin B1 on PMS symptoms among 210 female students (20.32 ± 8.92 years old). Participants were assigned in 3 groups of 70 individuals with the following regimen: group 1 received one pill containing 100 milligrams vitamin B1, group 2 received Ca pills and group 3 received placebo. The participants in all groups took medicines for 2 months and then reported the intensity of their symptoms by a questionnaire. Results of this study showed that both vitamin B1 and Ca reduce physical symptoms of PMS, but in terms of reducing psychological symptoms Ca was more effective.<sup>[25]</sup>

One year later, 66 female students (20.95 ± 1.19 years old) diagnosed with PMS were examined in another study. The participants were randomly assigned into two groups to receive 500 mg of Ca daily or placebo for 2 months. Significant differences were noticed between the two intervention groups in the first and second menstrual cycles after the intervention. The differences were significant ( $P < 0.05$ ) in subgroups of anxiety, depression, emotional changes, water retention, and somatic changes in Ca group compared with placebo in the menstrual cycle before the intervention and 2 menstrual cycles after the intervention and among menstrual cycles (0, cycle 1, cycle 2) in calcium group.<sup>[26]</sup>

Recently, Masoumi *et al.*, conducted a double blind randomized controlled trial on 76 students (21 ± 2.06 years old) with PMS. Students in group 1 received Ca tablet (500 mg) and vitamin B6 (40 mg) and subjects in group 2 received only vitamin B6 twice a day for two consecutive months. The results showed that although the severity of symptoms decreased in both groups, this reduction was more significant in the combined Ca and vitamin B6 group ( $P < 0.05$ ).<sup>[24]</sup>

Inconsistent with the above-mentioned studies is the evidence conducted by Yonkers *et al.* in 2013. A pilot study was conducted to compare fluoxetine and Ca to placebo in the treatment of premenstrual symptoms. Thirty-nine women (age range 25–45 years old) with at least 3 moderate to severe premenstrual symptoms and functional impairment received fluoxetine (10 mg twice daily), Ca

**Table 1: Characteristics of interventional studies**

Author, Year	Location	Sample size	Age range	Duration	Study Design	DAM	PMSAM	calcium dosage	Calcium type	Adjustment	Result	Quality score
Thys-Jacobs <i>et al.</i> , 1989	USA	60	35.1±6	3 months	RCT	Food record	PDSR	1000 mg daily	Calcium carbonate	Baseline symptoms score	Negative affect, water retention and pain reduced significantly	High
Thys-Jacobs <i>et al.</i> , 1998	USA	497	32.8±6.7	3 months	RCT	-	PMS Diary	1200 mg daily	Calcium carbonate	-	Total symptoms score reduced significantly	High
Ghanbari <i>et al.</i> , 2009	Iran	179	21.4±3.6	3 months	RCT	-	-	500 mg twice daily	Calcium carbonate	-	Tiredness, Appetite and Depressive symptoms reduced significantly	Low
Yonkers <i>et al.</i> , 2013	USA	39	25-45	4 months	RCT	-	Daily Record of Severity of Problems	600 mg twice daily	Calcium carbonate	-	NS	High
Bharati <i>et al.</i> , 2016	India	58	18-22	3 months	Quasi-experimental	-	-	500 mg daily	Calcium carbonate	-	Number and severity of PMS symptoms reduced significantly	Low
Samiepour <i>et al.</i> , 2016	Iran	210	20.32±8.92	2 months	RCT	-	PMS symptoms questionnaire	500 mg daily	Calcium carbonate	-	Physical, psychological and general symptoms of PMS reduced significantly	High
Masoumi <i>et al.</i> , 2016	Iran	76	21±2.06	2 months	RCT	-	PDSR	500 mg twice daily+ 40 mg vitamin B6	-	-	Physical, psychological and general symptoms of PMS reduced significantly	Low
Shobeiri <i>et al.</i> , 2017	Iran	66	20.95±1.19	2 months	RCT	-	Daily Record of Severity of Problems	500 mg daily	-	-	anxiety, depression, emotional changes, water retention, and somatic changes reduced significantly	High

DAM=Dietary Assessment Method, MSAM=Premenstrual Syndrome Assessment Method, PMS=Premenstrual Syndrome, RCT=Randomized clinical trial, PDSR=PMS Daily Symptom Record, GHQ-28=General Health Questionnaires-28, COPE=Calendar of Premenstrual Experiences, PSST=Premenstrual Syndrome Screening Tool, IU=International Unit



**Table 2: Characteristics of observational studies**

Author, Year	Location	Sample size	Age range	Study Design	DAM	PMSAM	Results	Quality score
Jacobs <i>et al.</i> , 1995	USA	12	28-45	Case-control	-	PMS Diary	Ionized calcium but not total calcium is lower in PMS subjects	Moderate
Shamberger <i>et al.</i> , 2003	USA	96	19-52	Case control	NM	NM	RBC total calcium is lower in PMS subjects	Moderate
Jacobs <i>et al.</i> , 2007	USA	115	26-31	Cross-sectional	Food record	PMS Diary	NS	Moderate
Saeedian Kia <i>et al.</i> , 2015	Iran	62	20-22	Case-control	24-hour recall questionnaire	Utah PMS Calendar II	Total calcium is lower in PMS subjects	Moderate
Bahrami <i>et al.</i> , 2018	Iran	897	12-18	Cross-sectional	-	COPE	There is no association between PMS and calcium except irritability	High
Fatemi <i>et al.</i> , 2019	Iran	278	19-21	Cross-sectional	-	PMS symptoms questionnaire	NS	Moderate

DAM=Dietary Assessment Method, MSAM=Premenstrual Syndrome Assessment Method, PMS=Premenstrual Syndrome, COPE=Calendar of Premenstrual Experiences, PSST=Premenstrual Syndrome Screening Tool, SRQ=Self-reported questionnaire, GHLQ=General health and lifestyle questionnaire, FFQ=Food Frequency Questionnaire, IU=International Unit, BMI=Body Mass Index

carbonate (600 mg twice daily), and placebo over the course of 4 menstrual cycles. In the Ca group during study period, there were no significant differences relative to placebo ( $P > 0.05$ ).<sup>[18]</sup>

### Observational studies

The association between serum calcium and PMS was investigated in 3 cross-sectional<sup>[17,30,31]</sup> and 3 case-control studies.<sup>[14-16]</sup>

In the first study, Thys-Jacobs *et al.*, observed Ca metabolism across one menstrual cycle in 12 healthy, premenopausal women (age range 28–45 years old). Seven women had documented PMS, and 5 were asymptomatic controls. Multivariate analysis indicated significant variation in total and ionized calcium across the menstrual cycle. Significant between-group differences were found for total calcium ( $P < 0.05$ ).<sup>[16]</sup>

A few years later, Shamberger *et al.* compared the levels of 18 red blood cell and 22 hair elements including calcium in 46 patients diagnosed with PMS and 50 normal subjects. Significantly lower amounts of calcium were screened in the blood of patients with PMS ( $P < 0.05$ ). The ratios of Mg/Ca were significantly higher in the PMS patients. The highly significant Mg/Ca ratio in blood cells may be indicative of a more complex relationship between PMS and Magnesium (Mg) and Ca than either element alone.<sup>[15]</sup>

Another evidence conducted by Saeedian Kia *et al.* which compared the nutritional status of vitamin D, Ca, and Mg in 62 students aged 20–25 years old (31 PMS cases and 31 controls), found lower serum levels of Ca in PMS participants as compared to healthy controls ( $P < 0.05$ ).<sup>[14]</sup>

In another study, Thys-Jacobs *et al.* measured fluctuations and group differences in Ca-regulating hormones across the menstrual cycle in women with and without premenstrual dysphoric disorder (PMDD). The PMDD group, when

compared with controls, had significantly lower ionized calcium at phase 1 and significantly lower urine calcium excretion at three of the five phases (late follicular phase 2, midcycle phase 3, and early luteal phase 4) ( $P < 0.05$ ).<sup>[30]</sup>

Bahrami *et al.* assessed the relationship between the menstrual bleeding pattern, PMS symptoms and Ca levels among 897 high school adolescent girls. It revealed an association between calcium level and menstrual blood loss and irritability but no other PMS symptoms.<sup>[17]</sup>

The last study examined the association between serum level of Ca and presence of PMS among 278 women (19–21 years old). It failed to show any association between Ca and PMS.<sup>[31]</sup>

### Discussion

To the best of our knowledge, this is the first systematic review evaluating the association between Ca and PMS in general population. Owing to the association between diets rich in dairy products and decreased PMS complications,<sup>[32]</sup> it is hypothesized that serum Ca level may be associated with the severity of PMS symptoms.

First section of our systematic review belongs to the observational studies with 4 of them showing lower serum Ca levels among PMS subjects.<sup>[27,29-31]</sup> Inconsistent with these, a study by Bahrami *et al.*<sup>[17]</sup> suggested a significant association between high corrected serum calcium and the incidence of irritability without any significant differences between the groups with regard to other physical or psychological symptoms of PMS. This discrepancy may be due to the different population samples; cycle regularity may be varying between younger and older women. Also, they found that in the hypercalcemia group, the majority of the participants presented moderate blood flow. The amount of blood loss during menstruation affects the overall quality of life of women,<sup>[33]</sup> so, this may be clinically relevant.

The other section of our review consists of interventional studies mostly reporting beneficial effects for Ca supplementation in PMS.<sup>[23-29]</sup> Only 1 pilot study reported small or no benefit of calcium as compared with placebo as a treatment for PMS.<sup>[18]</sup> However, the sample size for this pilot may not have been sufficient to draw definitive conclusions about treatment efficacy. Also, given that 1000 women were screened and slightly less than 5% were willing to participate in this pilot protocol, generalizability may be an issue with its results.

The characteristic feature of PMS is its occurrence during the luteal phase of the menstrual cycle with symptomatology unmasked, then remitting with the onset of menses. The most likely explanation for this temporal occurrence is the relationship between the ovarian steroid hormones and the calciotropic hormones. Ovarian steroid hormones, estrogens in particular, are known to influence the actions of the calciotropic hormones, specifically calcium and PTH.<sup>[7]</sup> Estrogen lowers serum calcium, and in its absence as seen at menopause, serum calcium concentrations rise.<sup>[9]</sup> Estrogen is believed to lower serum calcium through an inhibition of bone resorption by suppressing the mesenchymal process involved in bone remodeling and promoting bone mineralization.<sup>[34]</sup> Parathyroid hormone appears to act in an exactly opposite manner. Estrogen treatment in patients with mild primary hyperparathyroidism has been shown to lower serum and urinary calcium levels. Recent evidence suggests that estrogen has calcium antagonistic properties, inhibiting calcium currents and decreasing calcium entry into vascular smooth muscle.<sup>[35]</sup> During the menstrual cycle, estradiol has two peaks, one immediately before the LH surge and ovulation, and the second during the luteal phase. Increasing estrogen levels would result in falling calcium concentrations with compensatory rises in parathyroid hormone preventing marked degrees of hypocalcemia. Therefore, it may be hypothesized that women with an already underlying calcium disturbance, such as those suffering with PMS (lower calcium concentrations and higher PTH concentrations), would be subjected to further decrements in calcium concentrations on exposure to increasing estrogen levels during the luteal phase of the menstrual cycle. Since extracellular calcium is the ultimate source of intracellular calcium, intracellular calcium may be perturbed resulting in abnormalities of neurotransmitter synthesis and release. As a result, fluctuating estrogen levels in these women could alter serotonin receptor availability, binding and neurotransmission, which in turn can cause premenstrual mood symptoms.<sup>[36]</sup> It has been hypothesized that Ca supplementation could increase extracellular Ca which in turn may affect monoamine metabolism and reverse serotonin dysregulation.<sup>[5]</sup>

There are some limitations to this study that should be taken into account. First, most studies included in the systematic review had small sample sizes with short intervention

periods. Second, great differences in the studies in terms of statistical analyses or investigated exposures prevented us from doing meta-analysis. Third, except for one study which was established from Egypt, others were carried out in the United States and Iran which makes it difficult to generalize the results of this review to the rest of the world. On the other hand, inadequate calcium intake in the general population, especially among women, is a public health concern in developing countries, including Iran.<sup>[37]</sup> Therefore, the results need to be further investigated in populations with normal calcium levels. Besides, since PMS symptoms are recalled by the participants, recall bias is another limitation. Moreover, differences in the participants' diets might have affected serum levels of calcium in the studies that did not evaluate and control the women's diet.

According to what was discussed, it may be concluded that not only serum Ca levels are lower in PMS subjects, but also Ca supplementation could significantly improve the incidence of PMS and its related symptoms. However, based upon available evidence, we could not reach the overall results in the case of administered calcium dosage. Overall, in order to draw a firm link between Ca and PMS, further dose-response clinical trials with larger sample size and better methodology are warranted.

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### Conflicts of interest

There are no conflicts of interest.

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