Calcium Extended Abstract

Primary literature: Article #1

Ghanbari Z, Haghollahi F, Shariat M, Foroshani AR, Ashrafi M. Effects of calcium supplement therapy in women with premenstrual syndrome. Taiwan J Obstet Gynecol 2009 Jun;48(2):124-129.

Study objectives

To determine if there was any benefit of taking Calcium supplementation to help reduce the symptoms of PMS

Methods

- **Design**

  A randomized clinical trial
- **Allocation**

  There is no mention of allocation
- **Blinding**

  Both Participants and investigators were blinded, and the interventions were not revealed until after the study period concluded.
- **Follow – up period**

  There was no follow-up period; the study was conducted for a three month period.
- **Setting**

  The study took place at the Tehran Medical University, Iran in 2005. The participants were all female dormitory college students.
- **Participants**

  Female college students aged 21.4 (+/- 3.6 years) with criteria for PMS. Patients with any physical or psychological disorders were excluded, ”including depressive disorders, anxiety and panic disorders, migraine headache, irritable bowel syndrome,

asthma, chronic fatigue syndrome, thyroid and adrenal disorders, and the use of any medication or multivitamins." Prior to the study, the participant qualitative characteristics were similar.

- **Intervention**

  Patients either received 500mg calcium carbonate twice daily (Group B) or placebo (Group A) for three months.

- **Outcomes**

  The outcome measures were the intensity of the PMS symptoms "breast tenderness, fatigue, lack of energy, appetite changes, sleep problems, headache, depression, agitation, and irritability" as measured by questionnaires before and after and the intensity was self-rated on a scale of 1-3.

- **Patient follow – up**

  For the duration of the study, the participants were contacted each week and encouraged to continue to take their medication, however there was no follow-up upon completion of the trial.

Main Results

After treatment, there was a significant difference in the symptoms of tiredness ($p=0.029$), depression and sadness ($p=0.002$), and appetite improvements (0.004) in the calcium group compared to the placebo group. There was not a significant difference between the groups for breast tenderness, headache, anxiety, irritability, sleep changes, and lack of energy.

Conclusions

Overall, calcium supplementation for 3 months helped significantly improve the PMS symptoms of early tiredness, depression and sadness, and appetite.

Comments/critical appraisal (including assessment of internal and external validity)

The strengths of this study include randomization, double blinding, a moderate study size (n=179) and similar baseline characteristics amongst the participants for the criteria that was presented. Some of the weaknesses include: the baseline characteristics evaluated did not include many demographics such as ethnicity, physical activity levels, smoking, and other lifestyle considerations. The outcome was measured using a self-rated scale which had not been standardized, validated or evaluated for the symptoms of PMS, however the article just mentioned they were based on the Beck Test without providing a reference. The self-rated scale could introduce reporting bias as the questionnaires were conducted pre-study and post-study, so it is possible the patients inaccurately reported symptoms they experienced in the past three months if they had forgotten. There was no mention of the participants' diet and how much calcium was consumed in either group throughout the study duration. There was no mention of adverse effects or the safety of the medication or a method for participants to report these occurrences. There was also no mention if other self-selected medications were consumed during the duration of the trial. I would have also liked to have seen in the results section a question asking the participants to guess which group they were randomized to (either placebo or calcium) to get an understanding if the participants were truly blinded (Higgins, 2011). Overall, the internal validity was weak. In terms of external validity, the results could be applied to our patient population experiencing PMS, and due to the relatively safe profile of calcium as investigated by other studies (Thys-Jacobs et. al., 1998) the calcium supplementation could be recommended to females of similar age experiencing PMS symptoms. Overall, the study was of poor quality because the only outcomes measured were subjective questionnaires; however the study shows that there may be some benefit for patients experiencing PMS.

Primary literature Article #2

Thys-Jacobs S, Ceccarelli S, Bierman A, Weisman H, Cohen MA, Alvir J. Calcium supplementation in premenstrual syndrome: a randomized crossover trial. J Gen Intern Med 1989 May-Jun;4(3):183-189.

Study objectives

"To determine the efficacy of calcium supplementation in women with premenstrual syndrome"

Methods

- **Design**

  Randomized, double-blind crossover trial, ” placebo controlled
- **Allocation**

  There is no mention of allocation.
- **Blinding**

  Participants, evaluators, and the pharmacists dispensing the medication were blinded
- **Follow – up period**

  Participants were followed for the six months of treatment period and for an extra month post treatment
- **Setting**

  An Outpatient medical clinic at the Metropolitan Hospital in New York between January 1986 and February 1987
- **Participants**

  The participants were recruited by hospital staff and physician referral. **“**Seventy-eight women were initially screened. Trial selection was based on a history of recurrent PMS symptoms and on the results of a prospective assessment of daily symptom scores. Only women with symptom scores during the late luteal phase that were at least 50% greater than those during the intermenstrual phase were selected. Thirty-three women completed the trial.” Those enrolled were given instructions to avoid analgesics or NSAIDs for the duration of the trial. Exclusion criteria included: “elevated luteinizing hormone or follicular stimulating hormone… renal insufficiency, history of renal colic, nephrolithiasis, or hyperparathyroidism, involvement in an investigational drug study within four weeks of entry” and various other medical conditions. In total, 78 participants were screened, 60 were included, and only 33 women were analyzed in the study results, as many patients were lost for various different reasons (including compliance, alcohol, pregnancy, no benefit, adverse effects etc.)
- **Intervention**

  “A preliminary evaluation included physical examination, routine laboratory tests, dietary assessment, and psychiatric evaluation. Each participant included six months of treatment involving three months of daily calcium supplementation (1000mg of calcium carbonate) and three months of placebo.” Treatment started on the first day of menses. Participants were monitored at 1 month intervals. Participants were required to fill out daily questionnaires of 14 PMS symptom on a severity scale of 0-4.

- **Outcomes**

  The primary outcome measured was the daily ratings of symptoms and they were compared for both treatments. Each woman was her own control. Retrospectively, an overall global assessment was reported.

Main Results

Overall, a 50% decrease in symptoms resulted from calcium supplementation. The mean symptom scores decreased significantly when taking calcium compared to placebo for the luteal (7 days prior to menses, p=0.011) and menstrual (days of menstruation, p=0.032) phases. This wasn't observed intermenstrually (7 days after menstrual phase). Retrospective global assessment reveled 73% of women reported less symptoms while taking calcium (15% while taking placebo, and 12% no difference).

Looking at classes of symptoms (significance reported as p-value <0.05):

1) nervousness, irritability, mood, violence tendencies and depression were significantly reduced with calcium in the luteal phase;
2) fatigue, abdominal bloating, headache, and breast fullness were significantly reduced with calcium in the luteal phase;
3) increased appetite and craving for sweets **were not significantly reduced** in either phase; and
4) Abdominal cramps and back pain was significantly reduced with calcium in the luteal and menstrual phases.

Negative affect, water retention and pain were also significantly alleviated with calcium.

Conclusions

1000mg of Calcium supplementation daily was well tolerated and effective at reducing various symptoms of PMS in the luteal phase (7 days prior to menses).

Comments/critical appraisal (including assessment of internal and external validity)

A major strength of the trial was the trial included measures of dietary calcium. Baseline characteristics were similar. Another major strength was the crossover nature of the trial which eliminates confounding factors because all the participants received both placebo and calcium.

A weakness of this article is the poor attrition rate. Sixty patients were enrolled in the trial but only 33 fully completed the trial. A per protocol method of analyses was used which may result in an overestimation of treatment effect (due to a lower success of those who failed to complete the trial) so it would have been nice to see an intention-to-treat analysis. The study participants were mainly health care providers of Hispanic and black ethnicities perhaps making it difficult to apply to other population groups due to varying genetics. Due to the poor attrition rate and the low number of participants but strong study methods, the internal validity is moderate, and due to the difficulty of applying the results to the Canadian population, the external validity is weak.

Primary literature: Article #3

Thys-Jacobs S, Starkey P, Bernstein D, Tian J. Calcium carbonate and the premenstrual syndrome: effects on premenstrual and menstrual symptoms. Premenstrual Syndrome Study Group. Am J Obstet Gynecol 1998 Aug;179(2):444-452.

Study objectives

"To assess the effectiveness of calcium carbonate on the symptoms occurring during the luteal and menstrual phases of the menstrual cycle in women with PMS"

Methods

- **Design**
  "a prospective, randomized, double-blind, placebo-controlled,parallel-group, multicenter clinical trial"
- **Allocation**
  No mention of allocation
- **Blinding**
  Double-blinded
- **Follow – up period**

The patients were followed up for 3 months for the duration of the study (the participants were given 3 cycles to complete, and if needed, a fourth at max). They were contacted every 2 weeks via telephone, and every month on days 7 and 10 of their cycles.

- **Setting**

  The trial was a multicenter trial, conducted at **"**Six centers […](New York, New York; Lyndhurst, Ohio; New Haven, Connecticut; Levittown, New York; Cleveland, Ohio; Salt Lake City, Utah) and […](Spartanburg, South Carolina; Mobile, Alabama; New Orleans, Louisiana; Houston, Texas; Altamonte, Florida; Miami Beach, Florida)."

- **Participants**

  497 participants were enrolled, 466 patients met the criteria for analysis, and 441 patients completed 3 treatment cycles. **"**Healthy, premenopausal women between the ages of 18 and 45 years were recruited at 12 health centers." They were recruited via "advertisement, hospital newsletters, physician referral and word of mouth." Pre-screening was conducted to determine if the participants were willing to comply and to assess the degree of PMS. Inclusion criteria were evaluated for 2 cycles and included: good health from physical exams, blood and urine tests, regular cycles, discontinuation of analgesics for the trial, keeping a PMS diary evaluating 17 PMS symptoms, and a diagnosis of PMS. To qualify, the participants required an increase in intensity of symptoms of at least 50% during their luteal phases. The criteria is consistent with the National Institute of Mental Health Premenstrual Syndrome Workshop criteria. Exclusion criteria consisted of a variety of medical conditions, for example: renal colic, hypoparathyroidism, GI diseases, digitalis therapy, use of antacids, NSAIDS, diuretics, calcium channel blockers etc.. 231 patients were analyzed in the calcium group and 235 in the placebo group.

- **Intervention**

  One group received 1200mg of elemental calcium for 3 cycles, the other group received placebo (2x750mg of calcium carbonate twice daily). The patients recorded symptom severity, side effects, other medications taken, menstrual bleeding, compliance and how they felt daily. If the cycles were deemed non-evaluable, (meaning >20% of the days were non-evaluable due to, for example, non-compliance or they didn't record in the diary), the subjects could complete an extra cycle.

- **Outcomes**

  Primary outcome measure: symptom complex score (the average of the ratings for the 17 symptoms – "mood swings, depression-sadness, tension-irritability, anxiety-nervousness, anger-aggression–short temper, crying spells, swelling of

extremities, tenderness-fullness of breasts, abdominal bloating, lower abdominal cramping, generalized aches and pains, low backache, headaches, fatigue, increased or decreased appetite, cravings for sweets or salts, and insomnia")- the difference in symptom score (divided by 17) from the control to the intervention group. Secondary outcome measures were the use of rescue ibuprofen for pain, and the four symptom factors (negative affect, water retention, food cravings and pain)

Main Results

A significantly lower mean luteal symptom score was observed in the calcium group compared to the placebo group. By the third treatment cycle, calcium reduced the symptom score by 48% compared with 30% for placebo. This significant effect did not happen in the first cycle**.** By looking at each symptom individually, by the second and third cycles, all symptoms except for fatigue and insomnia showed a significant response to calcium treatment.

Calcium also significantly reduced the symptom factor scores during the luteal phase by the third treatment cycle (negative affect, water retention, food cravings and pain).

"Reported side effects were minimal, with the most commonly cited symptoms being headache, rhinitis, and pain." There were no significant differences in adverse events from each group.

Conclusions

Calcium treatment was effective for relieving the symptoms of PMS during the luteal phase and should be considered as an alternative therapy for PMS patients.

Comments/critical appraisal (including assessment of internal and external validity)

For the internal validity, this study conducted power calculations to determine the sample size required for showing significance which is a strong point; they recruited an adequate number of participants to take part in the trial (sample size was large, n=466). Baseline characteristics were similar, and baseline luteal symptom scores were for the most part similar for both groups (placebo and calcium). The trial was a multicenter trial which strengthens the internal validity. The follow-up was very complete and thorough.

The study compiled all 17 symptoms and took the average, although these symptoms are very different, and an average of 1 could mean the patient had mild 17 symptoms, or around 6 really severe symptoms (of which the patient presentation would look really different based on which symptoms they would be presenting with), thus it was great to see a breakdown of the symptoms individually as well. The study analyzed each symptom separately which is important instead of grouping them all together as we can better apply it to our patients, based on which symptoms our patients are experiencing. A weakness of the trial was that there was no mention of how the participants were randomized, if the allocation was concealed. There was no mention of tracking dietary calcium intake which could influence the results and perhaps lead to a larger treatment effect in either group. Although the study did take into consideration multiple disease conditions, medications, and use of oral contraception, there was no mention of lifestyle and other non-pharmacological measures patients may have used to reduce symptoms, for example exercise, smoking, drinking and other techniques. The outcome measures were also very subjective to the individuals in this trial as no objective measures of improvement in PMS symptoms were utilized, as seems to be the trend for PMS. Similarly to the other trials, there was no mention of the success of the blinding of participants. Overall, the internal validity was strong.

The study was mainly done using Caucasian participants and the results could apply to a similar patient in the 20-30s age range. Overall, the quality of this study was good as the treatment effect was large for many symptoms, the sample size was large, the study was randomized, blinded and it took into consideration multiple symptoms typical of PMS.

Secondary literature: article #4 (systematic review)

Whelan AM, Jurgens TM, Naylor H. Herbs, vitamins and minerals in the treatment of premenstrual syndrome: a systematic review. Can J Clin Pharmacol 2009 Fall;16(3):e407-29.

Study objectives

To systematically review the evidence for herbs, vitamins and minerals used to treat and reduce the symptoms of PMS.

Scope

The patients were either diagnosed with PMS, or had symptoms of PMS. The number of participants in the studies ranged from 1 participant to over 600. The majority of the treatments were compared to either placebo, to another non-prescription treatment option, and one trial compared the treatment to prescription fluoxetine therapy. Most of the trials were randomized controlled trials, and some were crossover trials. The duration of the trials were reasonable; the shortest trials were 2 months and the longest trials lasted 12 months, with the majority lasting 3-4 months. For calcium, 2 trials were included. The first trial was an 8 month crossover trial that was placebo controlled, enrolling 60 women whereas only 33 were included in the analysis. The outcome measured was the daily rating of severity of 14 PMS symptoms divided into 4 categories. Calcium significantly reduced symptoms compared to placebo in ¾ categories. In the other included trial that evaluated calcium, 497 women with diagnosed PMS were enrolled and 466 were used in the analysis. The outcome measured was the daily rating of 14 symptoms divided into 4 categories. Calcium significantly reduced symptoms compared to placebo. Both the trials included in this review have been critically appraised as a part of this extended abstract.

Methods

Firstly, the literature was searched to determine all the herbs and vitamins used to treat PMS. A library search was then conducted to identify RCTs by searching "Pubmed, Embase, International Pharmaceutical Abstracts, the Cochrane Library, Natural Medicines Comprehensive Database, and the International Bibliographic Information on Dietary Supplements (IBIDS)." The terms that were searched involved PMS and the herbals and vitamins used for treatment. Inclusion criteria was: RCTs, English or French, subjects with PMS, monotherapy (no combination products), and the outcome measure was the change in severity of symptoms. Exclusion criterion was: "Patient satisfaction survey as sole outcome measure; and not compared to placebo or recognized therapy." The review contained 29 articles for inclusion; these studies evaluated various options for PMS, such as chasteberry, evening primrose oil, gingko, saffron, St. John's Wort, Soy, Vitamin B6, Vitamin E, Calcium and Magnesium.

Main results

In both of the included trials that evaluated calcium, the treatment was found to be significantly better than placebo at reducing symptom severity ratings of PMS. The review concluded that the quality of both the trials was sufficient, and the results are applicable to practice. Only mild adverse effects of calcium were reported, such as nausea and headache.

Conclusions

Out of all the natural health products, vitamins and minerals, only calcium had good evidence to help reduce the symptoms of PMS, however further research is needed.

Comments/critical appraisal (including assessment of internal and external validity)

The meta-analysis only included two trials on calcium, and concluded that both trials were of sufficient quality. However, one trial (as mentioned earlier) had a poor attrition rate with a low number of participants (n=33). Also, both of the trials included were conducted by the same authors and both the trials had similar features, such as outcome measures using PMS symptoms divided into four categories. The only major differences in the trials were that one trial is a crossover trial with a small sample size, whereas the other trial was a larger multicenter trial. The trials were done by the same investigators thus it is expected that they would produce similar results; the evidence could be strengthened with further research from different investigators demonstrating that the results aren't specific to one study design, measures of outcome and reporting. Overall, the efficacy data is strong, and one of the trials was of good quality (but the other trial was weaker) so the results can be applied to clinical practice.

Secondary literature: Reference # 5 (systematic review and extended abstract)

Canning S, Waterman M, Dye L. Dietary supplements and herbal remedies for premenstrual syndrome (PMS): a systematic research review of the evidence for their efficacy. Journal of Reproductive and Infant Psychology.2006;24(4):363□378

Study Objectives: "To evaluate the effectiveness of dietary and herbal treatments for premenstrual syndrome (PMS)." (CRD reviewers, 2013)

Scope: The studies selected for the systematic review compared an active treatment for PMS to placebo or comparator for at least one cycle. The review looked at "calcium, vitamin B6, magnesium, evening primrose oil, Vitex agnus castus, St. John's Wort and gingko biloba" (CRD reviewers, 2013). The women in the trials were of reproductive age, with a diagnosis of PMS, without any psychiatric

conditions, unless the depression or anxiety was only premenstrually. The participants qualified with or without birth control. The duration of treatment ranged from one month to 12 months. 26 studies were included in this systematic review, of which only 2 were identified for calcium, as previously described above. The calcium studies included assessed PMS symptoms and conducted patient questionnaires as measured by patients. Both included calcium trials were 3 cycles in duration.

Methods: A search was conducted in **"**MEDLINE, EMBASE, AMED, CINAHL, PsycINFO and the Cochrane Controlled Trials Register" using a strategic search. "Crossover and parallel-group randomised controlled trials (RCTs) were eligible for inclusion in the review"(CRD reviewers, 2013).

Main Results: The studies selected were classified as either showing a positive treatment effect or a non-positive treatment effect. Both trials for calcium showed a positive effect (CRD reviewers, 2013). The first trial was positive for negative affect, water retention and pain. The second trial was positive for symptom complex scores and all symptom factors.

Conclusions – The study concluded that the two trials included for calcium were "well-designed" and that calcium was beneficial for the symptoms of PMS for three cycles.

Comments/critical appraisal (including assessment of internal and external validity) The authors described how they were assessing the trials however there was no mention about the criteria that was used to classify the trials (CRD reviewers, 2013). There was also no mention of how the studies were selected. The authors also did not describe how the data was extracted. The search criteria and terms used were well described. There was no statistics present on the tables of extracted study data, so it was difficult to understand the how significant the results were although the authors evaluated the significance using a checkmark or a cross which was easily interpreted (rather the extent of significance was more difficult to interpret). Overall, there was not a lot of description of how the data was extracted and assessed so it is difficult to know if the authors introduced biases (CRD reviewers, 2013). The conclusions for calcium are consistent with other primary and tertiary research.