

Calcium carbonate for premenstrual syndrome

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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;179:444-52.

Research question

Is calcium carbonate effective in decreasing symptoms of premenstrual syndrome (PMS)?

Type of article and design

Randomized, double-blind, placebo-controlled trial.

Relevance to family physicians

Premenstrual syndrome is common. An estimated 75% of women experience at least some premenstrual symptoms,¹ and up to 40% experience symptoms severe enough to affect daily life.² There is no single, widely accepted definition: both the tenth revision of the *International Classification of Diseases*³ and the American College of Obstetricians and Gynecologists⁴ have published criteria. There is consensus, however, that PMS is a collection of physical and psychological symptoms that occur during the luteal phase of the menstrual cycle and remit with or soon after onset of menses. Premenstrual dysphoric disorder (PMDD) is defined in the fourth edition of the *Diagnostic and statistical manual of mental disorders*⁵ and is usually thought of as a severe form of PMS. Only 3% to 8% of women fit the criteria for PMDD.¹

While there is evidence for use of selective serotonin reuptake inhibitor antidepressants in treating PMDD,⁶ many patients, especially those less severely affected, are reluctant to take such medications. Some women report improvement with oral contraceptives and nonpharmacologic lifestyle modifications, such as changes in diet, exercise, or stress management, but no research evidence supports these treatments. With the current popularity of alternative

health products, more and more patients are looking to vitamin or herbal remedies for relief.

This study examines use of calcium supplementation (in the form of TUMS EX[®]) as a treatment for PMS. The authors theorize that a pathophysiologic disturbance in calcium or parathyroid hormone regulation could be responsible for PMS. If effective, calcium would be an acceptable, accessible, and affordable option for many women.

Overview of study and outcomes

A 2-month screening phase was used to identify eligible women with moderate-to-severe PMS and to prospectively document baseline symptoms; 497 women aged 18 to 45 were finally enrolled in the study. Diagnosis was established with a PMS diary, a validated daily self-assessment questionnaire that asks women to rate 17 symptoms: mood swings, depression, tension, anxiety, anger, crying spells, swelling of extremities, breast tenderness, abdominal bloating, headaches, fatigue, increased or decreased appetite, cravings for sweets or salts, lower abdominal cramping, generalized aches and pains, low backache, and insomnia. To be eligible for the study, women had to record a 50% increase in symptoms during the luteal phase (the 7 days before menstruation) compared with the intermenstrual phase (the 7 days after menstruation).

Participants were randomly assigned to 1200 mg of elemental calcium or placebo daily. Treatment continued for three menstrual cycles. Women completed their PMS diaries each evening. Throughout the study, participants were asked to avoid analgesics except for ibuprofen, acetaminophen, or acetylsalicylic acid when symptoms were severe.

Inclusion criteria were general good health; regular menstrual cycles (every 23 to 38 days); normal complete blood count, blood chemistry, and urinalysis results; and negative results from a pregnancy test. Exclusion criteria were history

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of renal disease, renal colic, hypoparathyroidism or hyperparathyroidism, gastrointestinal or hepatic disease, chronic antacid use, use of bile acid resin binders, use of digitalis, calcium supplementation in excess of that found in multivitamins, serious gynecologic disease, active mental illness, pregnancy, breastfeeding, unwillingness to use acceptable contraception, use of oral contraceptives for less than 6 months before enrolment, and use of levonorgestrel implants.

Efficacy was determined by comparing subjects' mean symptom scores and percentage improvement between screening and treatment during luteal and intermenstrual phases in calcium and placebo groups.

Results

Of 497 women enrolled, 441 completed the trial, and 466 had sufficient data (defined as at least one screening and one treatment cycle) to be included in the analysis. All subjects who did not complete the trial or who were not included in the analysis were accounted for.

There were no differences between calcium and placebo groups with respect to age, height, weight, or oral contraceptive use. Both groups had similar symptom scores during all phases of the screening cycles. After 3 months of treatment, there was a 48% reduction in overall symptom scores during the luteal phase in the calcium group compared with a 30% reduction in the placebo group. Each of the 17 symptoms improved significantly with calcium by the third cycle, except for fatigue and insomnia.

Conversely, 8% of the women treated with calcium experienced a worsening of symptoms from baseline compared with 24% of the women treated with placebo. No differences in response to calcium treatment were detected between women who were taking oral contraceptives and those who were not.

Numerous minor adverse events were reported by 422 of the 466 patients. The most common events were headaches, rhinitis, and pain. Nausea prompted five women in the calcium group to discontinue the trial. One patient in each group developed renal calculi.

Analysis of methodology

Overall, this was a well designed study. Sample size was large, and many study centres were used. Symptoms of PMS are subjective, and use of a validated questionnaire, the PMS diary, helped strengthen documentation of treatment effect. Inclusion of a two-cycle screening phase allowed both identification of eligible patients and establishment of

baseline symptom scores. Compliance with treatment was monitored; 80% of tablets had to be taken or the cycle was deemed not able to be evaluated. Intention-to-treat analysis was used for all 466 subjects for whom data were available.

Limitations of the study include lack of documentation of dietary calcium intake. Could there have been a difference between groups in dietary calcium intake? Second, while use of analgesics was discouraged during the trial, extent of use was not documented. At least five of the 17 symptoms reported in the PMS diary might have improved with use of ibuprofen, acetaminophen, or ASA. Third, the trial was short, just 3 months, and treatment effects were most significant after 3 months. Would further improvements be noted over time? Would the effects wear off?

Fourth, intermenstrual phase symptom scores were not published in the study. I would have appreciated being able to review this information. While inclusion in the study required these scores to be 50% lower than luteal phase scores, it would be interesting to review whether symptoms during this phase of the menstrual cycle changed during treatment (symptoms should cease with menses or soon after^{3,4}). Pearlstein and Steiner have criticized this study for having possibly included subjects who had premenstrual exacerbation of chronic disorders rather than PMS.⁷

Finally, many adverse events were reported: 422 of 466 patients reported them. While there was no difference between treatment and placebo groups as to number of events reported and reported side effects were described as "minimal," a more detailed description of the nature of these events would be helpful for physicians considering recommending this treatment to their patients.

Application to clinical practice

Calcium supplementation is a simple, affordable, safe treatment option for many women who suffer from PMS. It might have the added benefit of preventing osteoporosis. I wonder what other effects an improvement in dietary calcium intake might have.

Bottom line

- Premenstrual syndrome is common.
- Supplementation with 1200 mg of elemental calcium per day might substantially decrease symptoms of PMS.
- Calcium supplementation must be taken for 3 months to achieve a treatment effect.
- Calcium supplementation might have secondary benefits in preventing osteoporosis. ❖

References

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Points saillants

- Le syndrome prémenstruel est fréquent.
- Un supplément de 1200 mg de calcium élémentaire par jour pourrait réduire considérablement les symptômes prémenstruels.
- Il faut prendre ce supplément de calcium pendant trois mois pour que le traitement fasse pleinement effet.
- Ce supplément de calcium pourrait avoir des bienfaits secondaires dans la prévention de l'ostéoporose.