Calcium carbonate and the premenstrual syndrome: Effects on premenstrual and menstrual symptoms

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OBJECTIVE: Previous reports have suggested that disturbances in calcium regulation may underlie the pathophysiologic characteristics of premenstrual syndrome and that calcium supplementation may be an effective therapeutic approach. To evaluate the effect of calcium carbonate on the luteal and menstrual phases of the menstrual cycle in premenstrual syndrome, a prospective, randomized, double-blind, placebo-controlled, parallel-group, multicenter clinical trial was conducted.

STUDY DESIGN: Healthy, premenopausal women between the ages of 18 and 45 years were recruited nationally across the United States at 12 outpatient centers and screened for moderate-to-severe, cyclically recurring premenstrual symptoms. Symptoms were prospectively documented over 2 menstrual cycles with a daily rating scale that had 17 core symptoms and 4 symptom factors (negative affect, water retention, food cravings, and pain). Participants were randomly assigned to receive 1200 mg of elemental calcium per day in the form of calcium carbonate or placebo for 3 menstrual cycles. Routine chemistry, complete blood cell count, and urinalysis were obtained on all participants. Daily documentation of symptoms, adverse effects, and compliance with medications were monitored. The primary outcome measure was the 17-parameter symptom complex score.

RESULTS: Seven hundred twenty women were screened for this trial; 497 women were enrolled; 466 were valid for the efficacy analysis. There was no difference in age, weight, height, use of oral contraceptives, or menstrual cycle length between treatment groups. There were no differences between groups in the mean screening symptom complex score of the luteal (P = .659), menstrual (P = .818), or intermenstrual phase (P = .726) of the menstrual cycle. During the luteal phase of the treatment cycle, a significantly lower mean symptom complex score was observed in the calcium-treated group for both the second (P = .007) and third (P < .001) treatment cycles. By the third treatment cycle calcium effectively resulted in an overall 48% reduction in total symptom scores from baseline compared with a 30% reduction in placebo. All 4 symptom factors were significantly reduced by the third treatment cycle.

CONCLUSIONS: Calcium supplementation is a simple and effective treatment in premenstrual syndrome, resulting in a major reduction in overall luteal phase symptoms. (Am J Obstet Gynecol 1998;179:444-52.)

Key words: Premenstrual syndrome, calcium supplementation, efficacy

The temporal occurrence and recurrence of mood and physical symptoms during the luteal phase of the menstrual cycle have been recognized for centuries. This phenomenon has come to be known as the premenstrual syndrome (PMS). For some women these somatic signals are minor disturbances that herald normal hormonal events culminating in menstruation. For others, these disturbances can be severe enough to disrupt their lives.[1]

In the past, therapies such as progesterone and vitamin B_6 were widely used forms of pharmacologic interventions in the management of PMS. Because scientific evidence in double-blind trials failed to prove these therapies of benefit,[2, 3] the therapeutic approach has now focused on medical and surgical ablation,[4] specifically, the gonadotropin-releasing hormone agonists,[5] the use of estradiol implants and patches,[6] and currently the use of serotonin reuptake inhibitors.[7]

Recent evidence has suggested that disturbances in calcium regulation may underlie the pathophysiologic characteristics of PMS and that calcium supplementation may be effective as a possible therapeutic approach to PMS. Two clinical investigations have shown calcium to relieve symptoms such as irritability, depression, anxiety, social withdrawal, headache, and cramps, all part of the

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symptom complex of PMS.[8, 9] In 1989, Thys-Jacobs et al[8] reported a significant 50% reduction in symptoms in 33 women with PMS in a double-blind, randomized, crossover trial on a daily calcium regimen of 1000 mg. Similarly, Penland and Johnson[9] in 1993 noted that increasing dietary calcium intake in the amount of 1336 mg/day in 10 women also reduced mood, pain, and water retention symptoms during the menstrual cycle. These treatment trials, however, consisted of small sample populations that may not have reflected general populations with diverse ethnic compositions. In support of these clinical observations, retrospective[10] and prospective[11] investigations have identified a relationship between PMS and bone loss, further promoting a derangement in calcium metabolism in PMS as a potential biologic trigger. Furthermore, one recent investigation[12] has suggested that exaggerated fluctuations of the calcium-regulating hormones across the normal menstrual cycle with a pattern of secondary hyperparathyroidism may precipitate the underlying disturbance in women with PMS. Therefore a clinical entity such as PMS could be a reflection of an important physiologic disruption in calcium balance, and adequate treatment of this imbalance could help restore bone mineral homeostasis and reverse the associated neuropsychiatric and physical disturbances.

On the basis of these observations, a randomized, double-blind, placebo-controlled multicenter trial was conducted 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

Subjects. Healthy, premenopausal women between the ages of 18 and 45 years were recruited at 12 health centers to participate in a randomized, double-blind, placebo-controlled study. Six centers were located above 40 degrees in latitude (New York, New York; Lyndhurst, Ohio; New Haven, Connecticut; Levittown, New York; Cleveland, Ohio; Salt Lake City, Utah) and 6 were below (Spartanburg, South Carolina; Mobile, Alabama; New Orleans, Louisiana; Houston, Texas; Altamonte, Florida; Miami Beach, Florida). Potential subjects were recruited by advertisement, hospital newsletters, physician referral, and word of mouth. Prescreening conducted by a trained clinical coordinator reviewed the subjects' willingness to comply with the study design and assessed, retrospectively, the severity and impact of PMS on the subjects' personal lives. This initial evaluation eliminated approximately two thirds of the potential subjects, resulting in 720 subjects accepted into the screening phase of the trial. Each woman with a history of cyclically recurring PMS was prospectively screened with a daily self-assessment questionnaire for 2 menstrual cycles. Inclusion criteria were (1) general good health as determined by history and routine physical examination, including a gynecologic examination and Papanicolaou smear, if one had not been performed within the past year; (2) laboratory evaluation, including normal findings of complete blood cell count, serum chemistry panel, and urinalysis and a negative pregnancy test result; (3) regular menstrual cycles of 23 to 38 days as documented in the daily diaries; (4) discontinuance of the use of analgesics (exclusionary medications), specifically, the nonsteroidal anti-inflammatory agents, for the duration of the study except rescue medication (allowable medication provided monthly to the subject for the relief of moderate to severe symptoms); and (5) the requirement that the diagnosis of PMS be prospectively documented for 2 menstrual cycles with the daily self-rating scale (the PMS Diary). Menstrual cycles were not to vary by more than ± 6 days for cycle lengths of 29 to 32 days. If a subject's cycle length fell outside of variation guidelines during the screening phase, a third screening cycle was offered. Once a subject was accepted into the treatment phase of the study, she was continued regardless of any variations in the cycle length. Before enrollment and treatment initiation, each woman underwent an extensive medical interview and physical examination with routine laboratory evaluation, including clinical chemistry, complete blood cell count, urinalysis, and pregnancy testing. All blood and urine specimens were evaluated in one central laboratory (Metpath Laboratories, Tetterboro, NJ).

Subjects were screened for a minimum of 2 menstrual cycles with the PMS Diary, a validated self-assessment daily diary.[13] The PMS Diary is composed of 17 items with 4 factor scales measuring negative affect, water retention, food, and pain. It is a single-page, self-report questionnaire using a 4-point rating scale from absent (0) to severe (3). The 17 symptoms evaluated were 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. Subject selection met the National Institute of Mental Health Premenstrual Syndrome Workshop criteria.[14] To confirm the diagnosis of PMS and qualify for enrollment, both a medical history of PMS with cyclically recurring symptoms rated at least moderate in severity and a 2-month prospective documentation of daily symptoms were required. A symptom-rating entrance criterion required a minimum symptom intensity increase of 50% in the luteal phase mean (7 days before menses) compared with the intermenstrual phase mean (7 days after menses) for both screening cycles. A third screening cycle was repeated if one set of screening diaries failed to meet entrance criteria. Subjects were discontinued from the trial if 2 screening

cycles failed to meet criteria. In addition, one or more of the following symptoms must have been present during the luteal phase for a woman to qualify: mood swings, depression-sadness, tension-irritability, anxiety-nervousness, anger-aggression–short temper, or crying spells. These entrance criteria were intended to be more rigidly exclusive than those proposed by the National Institute of Mental Health Premenstrual Syndrome guidelines.[14] Specific exclusion criteria included a history of renal disease, renal colic, hypoparathyroidism or primary hyperparathyroidism, significant gastrointestinal or hepatic disease such as active peptic ulcer disease, inflammatory bowel disease or malabsorption, chronic use of calcium-based antacids, digitalis therapy, use of bile acid resin binders, use of calcium supplements in excess of that found in multivitamins, significant gynecologic abnormality such as endometriosis, active mental illness including psychosis, pregnancy or breast-feeding, unwillingness to use an acceptable form of contraception, use of oral contraceptives for <6 months before study enrollment, and use of levonorgestrel (Norplant implants, Wyeth-Ayerst, Philadelphia).

Institutional review board approval was required before study initiation at all sites. Written informed consent was obtained from all study participants.

Study design. Sample size requirements were determined from a retrospective analysis of a previous clinical trial.[8] Approximating from that earlier study, we assumed an effect size of 2.0 units for the total mean symptom score with a common SD of 7.5 units. Setting type I error to .05 (two-tailed) and type II error set at .20, a sample size of 225 participants per treatment group was determined to be required in this trial.

After the initial 2-cycle screening phase, a total of 497 healthy premenopausal women who met all inclusion or exclusion criteria were enrolled in the treatment phase of the trial. Subjects were randomized into a double-blind, placebo-controlled, two-way parallel study. Two treatment groups were established. One group received 1200 mg of elemental calcium per day for 3 menstrual cycles. The other group was provided placebo. Subjects were instructed to take 2 tablets twice each day for the duration of the study. Each calcium tablet was provided in the form of 750 mg of calcium carbonate containing 300 mg of elemental calcium (TUMS E-X, SmithKline Beecham Consumer Healthcare, Pittsburgh). Each was informed to begin treatment 7 to 10 days after cessation of menses and then continue treatment daily for 3 menstrual cycles. Initiation of treatment was begun during the late follicular or early luteal phase of the menstrual cycle for the first treatment cycle only. Daily recording of symptoms, symptom severity, medication compliance, untoward side effects, medications other than treatment medication, and menstrual bleeding was to be completed each evening by the patient. Subjects were asked to complete the PMS Diary the same time each evening and were asked to rate how they felt over the previous 24 hours. Regular monitoring was conducted with biweekly telephone contact and monthly follow-up visits on days 7 to 10 of the menstrual cycle. After the initial 2 pretreatment visits, subjects were seen for a minimum of 4 further visits.

At each follow-up visit, treatment compliance was assessed. All unused medications were returned, collected, and counted by study coordinators. An 80% compliance rate with study medication was required for the cycle to be evaluable. PMS diaries were collected and evaluated, and new medications and diaries were dispensed. The number of unacceptable or nonevaluable days during treatment was recorded, and if the number of nonevaluable days for that cycle was determined to be >20%, subjects were offered an additional treatment cycle (not to exceed a total of 4 treatment cycles for the entire study). Days were considered unacceptable if patients had (1) taken exclusionary medication, (2) not completed the diary because of illness, (3) forgotten to record symptoms, or (4) forgotten to take the medication as prescribed. If the patient had ≥20% days in which she had not taken medication, the cycle was considered nonevaluable.

Concomitant therapy needed for treatment of underlying diseases or conditions was acceptable with the exception of nonsteroidal anti-inflammatory drugs, diuretics, digitalis, calcium channel blockers, and analgesics. Participants were instructed not to use any medications for pain relief during the trial, with the exception of rescue medication provided as a supply of ibuprofen. Patients were advised to use this medication only if necessitated by severe PMS symptoms. If ibuprofen was ineffective for a given patient, she was able to substitute either acetaminophen or aspirin.

Statistical analysis. All patients who were enrolled and had a valid screening cycle and a valid treatment cycle were included in the efficacy analysis. The primary outcome measure in the study was the symptom complex score, which was calculated as the average of the 17 daily individual symptom ratings. The primary measure of efficacy was the difference between the symptom complex score on active calcium treatment versus placebo. To simplify the numerics, the total score was divided by 17. The luteal mean symptom complex score was defined as the symptom complex score over 7 days before menses. (Thus a mean symptom complex score of 1.0 represented an average daily score of 17, either as 17 mild symptoms or 5.7 daily severe symptoms because a severe symptom was rated as 3.) The menstrual mean symptom complex score was defined as the symptom complex score over the actual number of days of menstruation. The intermenstrual mean symptom complex score was the symptom complex score over the 7 days after cessa-

Table I. Demographic data of study population by treatment group

	Calcium	*Placebo*	*Total*
No. of subjects	248	249	497
Age (y)	32.7 ± 6.7	32.9 ± 6.7	32.8 ± 6.7
Race			
White	202	197	399
Black	19	22	41
Asian	1	1	2
Hispanic	24	28	52
Other	2	1	3
Weight (kg)	65.8 ± 15.1	65.9 ± 15.3	65.9 ± 15.1
Height (cm)	163.8 ± 6.8	163.4 ± 6.7	163.6 ± 6.7
Oral contraceptives	29%	24%	26%
Cycle length (d)	29.3 ± 2.8	28.8 ± 2.6	29.1 ± 2.7
Bleeding length (d)	5.1 ± 1.3	5.2 ± 1.2	5.2 ± 1.3

Data are expressed as mean ± SD or percentage for yes-or-no answers.

Table II. Mean symptom complex scores for calcium and placebo treatment groups by specific treatment cycle and menstrual phase

Treatment group	*Mean screening*	*First treatment*	*Second treatment*	*Third treatment*
No of participants*				
Calcium	231	215	210	212
Placebo	235	220	224	228
Luteal				
Calcium	0.90 ± 0.52	0.58 ± 0.51	0.48 ± 0.46†	0.43 ± 0.40‡
Placebo	0.92 ± 0.55	0.66 ± 0.49	0.61 ± 0.48	0.60 ± 0.52
Menstrual				
Calcium	0.82 ± 0.54	0.60 ± 0.53	0.53 ± 0.47	0.47 ± 0.44
Placebo	0.81 ± 0.52	0.59 ± 0.50	0.54 ± 0.53	0.52 ± 0.52

Data are presented as mean ± SD.
*Number of participants with evaluable cycles.
†$P < .05$.
‡$P < .001$.

tion of menses. Mean cycle data were calculated for the screening and treatment cycles. The secondary outcomes were the rate of use of rescue medication and the 4 symptom factors (symptom factor 1 to symptom factor 4) as described elsewhere.[15] Symptom factors included negative affect, water retention, food cravings, and pain. Symptom factor scores were calculated as the average of the symptom scores for each symptom within the symptom factor group.

Comparability of treatment groups with respect to demographic and baseline characteristics was assessed with 1-way analysis of variance with treatment as the main factor for continuous variables or Fisher's exact test for discrete variables. The symptom complex score and 4 symptom factor scales, as well as individual symptoms, were analyzed with 2-way analysis of variance. The model variables for the analysis of variance were site, site by treatment interaction, and treatment in the model. Site and treatment were the main factors, and their interaction for each menstrual phase and cycle was analyzed separately. Sites 1 (Lyndhurst, Ohio) and 8 (New Orleans, Louisiana) had small sample sizes and were combined for the analyses. To confirm the nonsignificance of the results of the site by treatment interaction in the 2-way analysis of variance, each site was analyzed separately for the symptom complex score and for the 4 symptom factor scales with 1-way analysis of variance. The percent change from baseline was characterized into 4 groups: percent negative improvement, >0% to <50% improvement, ≥50% improvement, and ≥75% improvement. In addition, a subgroup analysis for assessing the consistency between use and nonuse of oral contraceptives was conducted for the symptom complex score and 4 symptom factor scales. Because we were interested in geographic and seasonal differences in baseline symptom scores, we analyzed the differences between the northern site versus the southern site and the effect of seasonal change on treatment effect.

Statistical significance was determined on the basis of 2-tailed tests at P values < .05.

Results

Seven hundred twenty women were screened. Four hundred ninety-seven patients were enrolled in the study; 466 met criteria for efficacy analysis (1 screening and 1 treatment cycle). Of the 31 patients not included

Table III. Calcium treatment on 4 symptom factor scores

Factor and symptoms	*Treatment group*	*Luteal phase symptom factor score*		*Menstrual phase symptom factor score*	
		Mean screening	*Third treatment*	*Mean screening*	*Third treatment*
Symptom factor 1: Negative affect	Calcium	0.99 ± 0.59	0.46 ± 0.47*	0.77 ± 0.62	0.40 ± 0.47
Mood swings	Placebo	1.04 ± 0.66	0.65 ± 0.64	0.80 ± 0.62	0.48 ± 0.57
Depression					
Tension					
Anxiety					
Anger					
Crying spells					
Symptom factor 2: Water retention	Calcium	0.96 ± 0.58	0.51 ± 0.46*	0.93 ± 0.60	0.59 ± 0.54
Swelling of extremities	Placebo	0.97 ± 0.60	0.69 ± 0.58	0.92 ± 0.57	0.63 ± 0.61
Tenderness of breasts					
Abdominal bloating					
Headache					
Fatigue					
Symptom factor 3: Food cravings	Calcium	0.97 ± 0.76	0.45 ± 0.63†	0.78 ± 0.68	0.40 ± 0.61
Increased or decreased appetite	Placebo	1.02 ± 0.76	0.60 ± 0.75	0.73 ± 0.64	0.42 ± 0.64
Cravings for sweets or salts					
Symptom factor 4: Pain	Calcium	0.74 ± 0.63	0.30 ± 0.40*	0.94 ± 0.65	0.52 ± 0.55
Lower abdominal cramping	Placebo	0.69 ± 0.58	0.50 ± 0.52	0.87 ± 0.60	0.58 ± 0.60
Generalized aches and pains					
Low backache					

Data are presented as means ± SD.
*$P < .001$.
†$P < .05$.

in the efficacy analysis, 17 had insufficient data to analyze, 13 had 1 or 2 treatment cycles that were nonevaluable, and 1 patient had 2 invalid screening cycles and was incorrectly enrolled in the study. Of the remaining 466 patients, 441 patients (95%) completed the trial with 3 out of 4 possible treatment cycles. Of the 25 patients who did not complete the trial, 15 patients had only 1 treatment cycle; 10 patients had only 2 treatment cycles. There were 231 patients in the calcium treatment group and 235 in the placebo group.

The demographics of the patients for the calcium and placebo groups are summarized in Table I. The ages of the participants ranged from 18 to 45 in years. No differences existed in age, height, weight, or birth control use between the 2 treatment groups. The most frequently observed menstrual cycle length was 27 to 29 days, with the most frequent menstrual bleeding length of 5 days. No difference existed between groups in either cycle length or menstrual bleeding length. Of the study population enrolled, 28% began treatment in February, 20% in March, and 56% between the months of January and March.

Results of the analysis of variance by mean cycle (treatment or screening) and menstrual phase (luteal and menstrual) for symptom complex score are listed in Table II. No significant differences were found between groups for the mean screening of the luteal ($P = .659$), menstrual ($P = .818$), or intermenstrual phase ($P = .726$) of the cycle. The baseline luteal mean symptom complex scores were 0.90 ± 0.52 for the calcium treatment group and 0.92 ± 0.55 for the placebo group. During the treatment cycle a significantly lower symptom complex score was observed in the calcium-treated group for both the second and third treatment cycles during the luteal phase ($P < .05$, $P < .001$). The luteal phase symptom complex score by the third calcium treatment was 0.43 ± 0.40 compared with the placebo treatment symptom complex score of 0.60 ± 0.52. For the placebo group the luteal mean symptom complex score values during the treatment cycle were lower when compared with the screening values but remained at similar levels for the 3 treatment cycles. The luteal mean symptom complex score values for the calcium group were lower for the treatment cycles compared with the symptom complex score values during screening, and these mean symptom complex scores progressively decreased for each treatment group. By the third treatment cycle calcium effectively reduced the symptom complex score by 48% compared with the placebo effect of 30%. This significant calcium effect was not detected in the first treatment cycle when calcium treatment was initiated well into the latter part of the menstrual cycle. Nor was this effect noted during either the menstrual or intermenstrual phase of the menstrual cycle.

The results of the effect of calcium treatment on the symptom factors (symptom factors 1 to 4) are shown in Table III. As noted with the mean symptom complex score, a significant calcium effect on all 4 symptom factors was observed during the luteal phase of the menstrual cycle. No significant effect was noted during the

Table IV. Differences between treatment groups during luteal phase for individual symptom complex scores

	Baseline			*Third treatment cycle*		
	Mean symptom complex score			*Mean symptom complex score*		
Symptom	*Calcium group*	*Placebo group*	*Statistical significance*	*Calcium group*	*Placebo group*	*Statistical significance*
1. Mood swings	1.06 ± 0.70	1.11 ± 0.77	$P = .484$	0.50 ± 0.58	0.70 ± 0.75	$P = .002$
2. Depression-sadness	0.94 ± 0.66	0.95 ± 0.75	$P = .809$	0.43 ± 0.55	0.58 ± 0.74	$P = .011$
3. Tension-irritability	1.31 ± 0.68	1.39 ± 0.71	$P = .331$	0.62 ± 0.58	0.84 ± 0.77	$P < .001$
4. Anxiety-nervousness	0.98 ± 0.77	1.03 ± 0.83	$P = .359$	0.45 ± 0.58	0.66 ± 0.77	$P < .001$
5. Anger–short temper	1.14 ± 0.68	1.20 ± 0.77	$P = .470$	0.53 ± 0.57	0.74 ± 0.77	$P = .001$
6. Crying spells	0.51 ± 0.58	0.56 ± 0.65	$P = .237$	0.23 ± 0.40	0.37 ± 0.57	$P = .002$
7. Swelling of extremities	0.77 ± 0.75	0.74 ± 0.72	$P = .701$	0.40 ± 0.57	0.56 ± 0.70	$P = .007$
8. Tenderness–breast fullness	1.10 ± 0.85	1.18 ± 0.82	$P = .228$	0.59 ± 0.67	0.84 ± 0.77	$P < .001$
9. Abdominal bloating	1.12 ± 0.72	1.12 ± 0.75	$P = .818$	0.55 ± 0.63	0.81 ± 0.77	$P < .001$
10. Abdominal cramping	0.70 ± 0.66	0.73 ± 0.68	$P = .741$	0.29 ± 0.44	0.50 ± 0.59	$P < .001$
11. Aches and pains	0.70 ± 0.68	0.66 ± 0.63	$P = .469$	0.31 ± 0.49	0.49 ± 0.60	$P < .001$
12. Low backache	0.82 ± 0.74	0.69 ± 0.66	$P = .033$	0.30 ± 0.45	0.49 ± 0.59	$P < .001$
13. Headaches	0.73 ± 0.66	0.76 ± 0.66	$P = .445$	0.40 ± 0.52	0.52 ± 0.58	$P = .033$
14. Fatigue	1.09 ± 0.72	1.05 ± 0.72	$P = .573$	0.60 ± 0.66	0.71 ± 0.73	$P = .135$
15. Appetite increased or decreased	0.97 ± 0.78	1.03 ± 0.77	$P = .483$	0.46 ± 0.65	0.61 ± 0.76	$P = .025$
16. Craving sweets or salts	0.97 ± .80	1.02 ± 0.79	$P = .597$	0.43 ± 0.64	0.60 ± 0.78	$P = .010$
17. Insomnia	0.36 ± 0.55	0.38 ± 0.59	$P = .469$	0.15 ± 0.35	0.19 ± 0.41	$P = .213$

Data are expressed as mean ± SD.

menstrual or intermenstrual phase of the cycle for the symptom factors. Three of the 4 symptom factors (symptom factor 1, symptom factor 2, symptom factor 4) were observed to have significantly lower symptom factor scores by the second treatment month. There were significantly lower symptom scores for all 4 factors (negative affect, symptom factor 1 [$P < .001$]; water retention, symptom factor 2 [$P < .001$]; food cravings, symptom factor 3 [$P < .05$]; and pain, symptom factor 4 [$P < .001$]) by the third calcium treatment cycle compared with placebo. By the third treatment cycle the negative affect symptom factor was reduced by 45% for calcium compared with 28% for placebo, the water retention symptom factor was reduced by 36% for calcium compared with 24% for placebo, the food cravings symptom factor was reduced by 54% compared with 34% for placebo, and the pain symptom factor was reduced by 54% compared with –15% for placebo (pain symptoms were worse on placebo). None of the symptom factors was significantly different from placebo during the acute phase or first treatment cycle.

All 17 individual symptoms were analyzed to determine differences between treatment groups during the luteal phase of the menstrual cycle. With the exception of low backache, no significant differences were found between treatment groups in individual symptom scores during the mean screening. Within the first treatment cycle, only the individual symptom of generalized aches and pains proved significantly different from placebo (0.41 ± 0.62 vs 0.55 ± 0.64, $P = .031$). By the second and third treatment months all symptoms except for fatigue and insomnia showed a significant response to calcium treatment (as shown in Table IV). For the symptom of low backache, the mean screening calcium score was significantly higher than the placebo group score (0.82 ± 0.74 vs 0.69 ± 0.66, $P = .033$) and became significantly lower than the placebo group score by the end of the third treatment cycle (0.30 ± 0.45 vs 0.49 ± 0.59, $P < .001$).

An analysis of the frequency of percent improvement and percent negative change by the third treatment cycle showed the following distribution: 8% of the women receiving calcium treatment had negative improvement or worsening of the baseline symptoms compared with 24% of the women receiving placebo, 55% given calcium had >50% improvement in global symptoms compared with 36% given placebo, and 29% given calcium had >75% improvement in global symptoms compared with 16% receiving placebo. More than 50% of the women given calcium treatment had >50% improvement in all 4 factors; 60% of the women had >50% improvement in pain symptoms. Analysis of the percent negative improvement group (those women whose symptoms were worse at the end of the trial than at baseline screening) revealed a subset of 71 women, 17 of whom had been given calcium treatment and 54 who received placebo. Three times as many women experienced worsening of their symptoms with placebo compared with calcium.

A subgroup analysis was performed on oral contraceptive users and nonusers to evaluate the effect of calcium in these two groups separately (data not shown). No difference was found in luteal mean screening scores between the calcium versus placebo treatment arms in either nonuser or user groups (nonusers, $P = .682$; users, $P = .466$). At the end of the treatment trial the calcium effect was significant in both the nonuser group and the

user group ($P < .001$ and $P = .05$, respectively). Although the significant calcium effect in the nonuser group was much stronger than in the user group, this study was not sized to determine clinical relevance in a separate subgroup.

A total of 422 patients reported adverse events during the study, 216 for the calcium group and 206 for the placebo group. Reported side effects were minimal, with the most commonly cited symptoms being headache, rhinitis, and pain. No statistically significant differences were found between the 2 treatment groups in the reporting of these events or in the use of rescue medication. A total of 16 subjects were discontinued from treatment because of an adverse event. Five patients were from the placebo group and 11 were from the calcium group. Five patients were discontinued from the calcium treatment group because of nausea. In 2 patients kidney calculi developed during the treatment trial; 1 was given placebo and the other calcium. The remainder of the subjects who discontinued the trial cited menorrhagia, pinched nerves, or emergency surgery as adverse events.

When we analyzed the differences in northern versus southern sites, significantly lower symptom complex scores were detected in the southern sites during the first treatment phase with calcium and during the final treatment phase (data not shown). In addition, lower symptom complex scores were noted for the placebo group in the southern states compared with the northern states during the second and third treatment phases. Seasonal differences in calcium treatment effect were not detected because of major treatment initiation during the winter months and inadequate subsets in the remaining seasons.

Comment

PMS afflicts millions of premenopausal women[1] and has been described as one of the most common disorders in women. Despite its overwhelming prevalence, clinical investigations exploring its pathophysiologic features have been disappointing. Multiple investigations of basal levels of gonadal steroid hormones, gonadotropins, thyroid, and other hormones have not detected differences between women who have symptoms and those who do not.[16] Few therapeutic modalities have proved consistently effective.[2, 4]

This study has found that calcium supplementation effectively alleviates the luteal phase symptoms of PMS. Calcium treatment resulted in an approximately 50% reduction in total mean symptom scores with a significant benefit on symptoms such as depression, mood swings, headache, and irritability. Calcium was effective on all 4 core symptom factors of PMS representative of this syndrome (negative affect, water retention, food cravings, and pain) and on 15 of the 17 individual symptoms. The findings in this large study are consistent with an earlier trial reporting a significant benefit with the use of calcium therapy in women with PMS.[8] Calcium was not found effective during the menstrual or intermenstrual phase of the cycle.

Some investigators have defined clinical relevance as percent improvement from baseline in luteal phase symptom scores. In such studies a 50% improvement from baseline represented moderate symptom improvement.[17] In our trial we did not define clinical relevance as percent improvement, although we did analyze for percent improvement and percent symptom reduction. The percent improvement changes in our trial (55% of the women given calcium treatment experienced >50% improvement in global symptoms vs 36% of the women given placebo) are comparable to those in other large clinical trials in the treatment of PMS and premenstrual dysphoria. In a double-blind, placebo-controlled, parallel-designed study of oral progesterone, alprazolam, and placebo in the treatment of PMS, changes from baseline symptom scores were reported as percentages of improvement, with 37% of the subjects experiencing a 50% improvement on alprazolam.[18] The absolute percent symptom reduction was not reported in that trial. However, on the basis of the mean symptom score data presented in their investigation, an approximately 40% reduction in premenstrual symptoms was demonstrated with alprazolam compared with a 25% reduction for placebo. In our trial we found a 48% symptom reduction in the calcium group compared with 30% in the placebo group. Similarly, in a large multicenter, double-blind trial involving the serotonin reuptake inhibitor fluoxetine in the treatment of premenstrual dysphoria, Steiner et al[19] enrolled 405 women (180 completed) and noted a significant reduction in symptoms (specifically, the negative affective symptoms of tension, irritability, and dysphoria) as measured by a visual analog scale. By the end of treatment cycle 6 a 44% symptom reduction with fluoxetine treatment was demonstrated compared with 24% for placebo. Our trial investigated subjects with PMS and not specifically premenstrual dysphoria. However, our percent symptom reduction for negative affect symptoms consisting of mood swings, depression, tension-irritability (45% reduction for the negative affect symptom factor compared with 28% reduction for placebo) is similar to that reported by Steiner's group. The effect of calcium treatment appears comparable to that of the serotonin reuptake inhibitor fluoxetine for negative affect symptoms and to that of the anxiolytic alprazolam for the syndrome. In our trial the placebo effect of 30% was considerable but comparable to the results reported in other clinical trials investigating treatments for PMS and depression.[18]

The advent of gonadotropin-releasing hormone agonists that suppress ovulation by inhibiting the release of gonadotropins has provided an important tool in the

treatment of severe PMS. They have been reported to reduce PMS symptoms by 75%, but because of their hypoestrogenic effects, they increase the risk of bone loss, worsen mood and depression symptoms, result in unacceptable compliance and dropout rates, and are very costly.[5] Selective serotonin reuptake inhibitors have also proved to be an effective therapy in some women with PMS, specifically those with premenstrual dysphoria.[20] However, in 1 placebo-controlled study involving the serotonin reuptake inhibitor fluoxetine, the side effects (insomnia, nausea, tremor, dizziness) and the lack of efficacy resulted in a significant dropout rate of 42%.[19] In contrast to the gonadotropin-releasing hormone agonists and the serotonin reuptake inhibitors, calcium therapy is inexpensive, does not result in bone loss, is effective on mood and depression, as well as on all 4 symptom factors, and did not result in significant noncompliance because of adverse events.

Calcium excretion was not measured during the course of this clinical trial, and therefore the presence or absence of hypercalciuria was not determined. Renal stones developed as an adverse event in only 2 subjects, 1 in the calcium treatment group and 1 in the placebo treatment group. The level of calcium supplementation in this study (1200 mg/day) was within the range tested in 2 smaller studies that have examined the use of calcium supplementation in the relief of PMS symptoms.[8, 9] The recently revised adequate intake levels for calcium include targets of 1300 mg/day for girls 14 through 18 years old and 1000 mg/day for women 19 through 50 years old.[21] Median calcium intake for these groups is estimated at less than two thirds of adequate intake, with the adequate intake met only by those above approximately the 95th percentile of calcium intake. The same revision established a tolerable upper intake limit, the maximum level unlikely to cause adverse health effects, at 2500 mg/day. Thus the level of calcium supplementation consumed in this study is judged to be safe. Ideally, calcium supplements should be consumed with meals to bind dietary oxalate, reducing its absorption and renal excretion and thereby protecting against nephrolithiasis.

The pathophysiologic characteristics in PMS have yet to be clearly defined. Recent evidence has suggested that abnormalities in calcium and vitamin D regulation may be responsible for the clinical manifestation of PMS.[12] In 1 investigation calcium and vitamin D replacement reversed the abnormal responsiveness to the calcium-regulating hormones during the menstrual cycle, possibly explaining the alleviation of symptoms noted with this therapy. In the prototypical calcium disorder primary hyperparathyroidism, elevated parathyroid hormone concentrations have been associated with neuropsychiatric disturbances such as depression and psychosis.[22] Recent investigations have suggested that disturbances in either intracellular calcium or parathyroid hormone in patients with primary hyperparathyroidism may result in low cerebrospinal fluid concentrations of monamine metabolites such as 5-hydroxyindole acetic acid.[23] As with primary hyperparathyroidism, the affective symptoms of PMS have recently been linked to monoamine metabolism and serotonergic dysregulation.[24] Calcium may ultimately affect the monoamine metabolism reversing the serotonergic dysregulation and providing a biochemical basis for the therapeutic effect.

Interestingly, another important divalent intracellular cation, magnesium, has been proposed to precipitate PMS in the setting of a deficiency state. Several reports[25] have cited lowered magnesium levels in the erythrocytes of women with PMS despite normal extracellular concentrations. Oral magnesium supplementation in 1 small double-blind trial[26] was shown to relieve the negative affective symptoms in women with PMS. Severe magnesium deficiency is known to disturb mineral homeostasis and may result in a secondary hyperparathyroidism or hypoparathyroidism manifesting as neuromuscular irritability and symptoms reflective of the PMS.

In conclusion, this multicenter study has found that calcium carbonate was an effective treatment for all the core symptom factors characterizing the PMS during the luteal phase of the menstrual cycle and should be considered an alternative therapeutic approach in the management of PMS. Calcium supplementation may act by repleting an underlying physiologic deficit, suppressing parathyroid hormone secretion, and, ultimately, reducing neuromuscular irritability and vascular reactivity. Should PMS prove to be an indicator of low calcium status that encourages premenopausal women to increase their calcium intake, the public health benefit in areas such as osteoporosis risk reduction could be significant. Further investigations into adequate dose and duration of therapy may provide further benefits for women with PMS.

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