

EFFECTS OF CALCIUM SUPPLEMENT THERAPY IN WOMEN WITH PREMENSTRUAL SYNDROME

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SUMMARY

Objective: Scientific evidence suggests that cyclic fluctuations in a variety of nutrients, especially calcium, may help to explain some features of premenstrual syndrome (PMS). We determined the efficacy of calcium supplementation in women suffering from PMS.

Materials and Methods: A double-blind clinical trial was designed to evaluate the effect of calcium supplement therapy on PMS symptoms. The study groups were selected from young female college students, based on PMS criteria. The subjects were divided in two groups; one group received placebo and the other received 500 mg of calcium carbonate twice daily for 3 months. The severity and intensity of symptoms, including early fatigability, changes in appetite, and depression, were evaluated using a standard questionnaire. Symptoms were compared before and after treatment.

Results: The mean age was 21.4 ± 3.6 years. Early tiredness, appetite changes, and depressive symptoms were significantly improved in the group receiving calcium treatment compared with the placebo group.

Conclusion: Our results showed that calcium supplements reduced early fatigability, changes in appetite, and depression in women with PMS. [*Taiwan J Obstet Gynecol* 2009;48(2):124-129]

Key Words: calcium supplementation, female students, premenstrual syndrome

Introduction

Premenstrual syndrome (PMS) is the cyclic appearance of one or more of a group of symptoms just before each menses, to a degree that can affect the sufferer's quality of life. The most frequent symptoms include abdominal bloating, breast tenderness, anxiety, crying spells, depression, fatigue, lack of energy, anger and irritability, changes in appetite, and varying degrees of edema [1].

The prevalence of PMS during the reproductive period has been reported to be between 70% and 90% [2]. Diagnosis requires the presence of at least one

symptom of somatic or mood disorders occurring during 3 consecutive months, beginning during the last week of each cycle and interfering with work or usual activities, and remitting after each menses [3]. Based on a study performed in 2004 [4], women with PMS had more work absences than those without PMS (7.3 vs. 2.5 days; $p = 0.006$). Women with PMS also had more days of disturbances during their school work or jobs compared with those without PMS [4].

Thys-Jacobs et al [2] demonstrated a relationship between hypocalcemia and PMS symptoms, including fatigue, anxiety, depression, mood changes, and muscle cramps. They suggested that PMS symptoms were equivalent to signs of osteoporosis during menopause. Shamberger [5] revealed that levels of calcium and some trace elements in red blood cells were lower than normal in women with PMS. A relationship between intracellular calcium concentration and mood disorders in PMS has been demonstrated during the last 50 years



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[6]. Changes in extracellular calcium concentration could have stimulatory effects on neuromuscular junctions [7], and irritability, mania and agitation have been reported in conjunction with hypocalcemia [8]. Based on these observations, we evaluated the efficacy of 500 mg of calcium carbonate twice a day for 3 months on reduction of PMS symptoms.

Materials and Methods

This randomized, double-blind clinical trial was performed during 2005. We selected female college students who were living in the dormitory of Tehran Medical University. Exclusion criteria were any kind of physical or psychologic disorder included in the differential diagnosis of PMS, 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. Five hundred students filled out a primary questionnaire. Of these, 260 met the criteria for PMS and were enrolled in this study. Some failed to complete the study and were excluded, leaving a total of 179 students. After obtaining written legal and moral consent, they were randomly divided into two groups. There were 88 students in Group A and 91 in Group B. One group (blindly) received 3 months of treatment with 500 mg of calcium carbonate twice a day while the other group received a placebo. Both placebo and calcium carbonate were produced by the pharmaceutical company, Tehran Chimi, Iran. Both groups were given their medication or placebo by a medical trainee, and they were contacted each week during the study to encourage them to continue their medication. At the end of the treatment period, they filled out a second questionnaire to evaluate changes in the intensity of their symptoms. Both the initial and the second questionnaires were designed based on the Beck test, and the intensity of the symptoms was scored from 0 to 3. The data were analyzed with χ^2 test, *t* test, paired *t* test, and McNemar test, using SPSS version 11 (SPSS Inc., Chicago, IL, USA).

The PMS symptoms evaluated included breast tenderness, fatigue, lack of energy, appetite changes, sleep problems, headache, depression, agitation, and irritability.

Results

At the end of the study, the company revealed that Group A had received the placebo and Group B had

received the calcium tablets. The mean age for both groups was the same (21.4 ± 3.6 years). All physical and psychologic symptoms were similar in both groups (Table 1).

Before treatment, 47.7% of the women in Group A and 57.1% in Group B suffered from breast tenderness ($p=0.20$; Table 1). After treatment, these values were 51.1% in Group A and 57.1% in Group B ($p=0.42$; Table 2).

Before treatment, 60.5% of Group A and 72.2% in Group B suffered from early tiredness. After treatment, the incidence of early tiredness fell to 52.3% in Group A, and 36.0% in Group B ($p=0.029$; Table 3). The McNemar test revealed that the incidence of early tiredness was significantly reduced in Group B after treatment (from 72.2% to 36.0%; $p<0.001$), while the incidence in Group A showed no significant reduction ($p=0.37$).

Lack of appetite was observed in 81.8% of women in Group A and 77.0% in Group B before intervention ($p=0.370$; Table 1). After treatment, lack of appetite was found in 75.0% of women in Group A and 52.7% in Group B ($p=0.004$; Table 2). These results suggest that the treatment in Group B was more effective than that in Group A.

The incidence of premenstrual headache was similar in both groups before treatment (Table 1), and there was no significant change after treatment in either group ($p=0.66$; Table 2).

Before treatment, anxiety and agitation were observed in 61 women (70.9%) in Group A and 63 (69.2%) in Group B. After treatment, 68.6% in Group A and 65.2% in Group B still suffered from this symptom ($p=0.62$; Table 2), suggesting no effect of the intervention on anxiety and agitation.

As shown in Table 1, irritability was observed in 80.2% of women in Group A and 87.9% in Group B before treatment. After treatment, these were reduced to 54.7% in Group A and to 42.7% in Group B. Comparison between the two groups after treatment revealed no significant difference, but the McNemar test showed a meaningful reduction in incidence (25.5% in Group A and 45.2% in Group B) following treatment in both groups, suggesting that both calcium and placebo effectively reduced irritability (Table 2).

There were no significant differences in sleep patterns (insomnia, hypersomnia or hyposomnia) before (Table 1) and after treatment (Table 2).

Lack of energy before each menses was experienced by 60.5% of women in Group A and 60.4% in Group B (Table 1). After intervention, 34.9% in Group A and 32.2% in Group B still showed this symptom. There was no significant difference between the groups ($p=0.7$;

Table 1. Frequency distribution of qualitative variables in Groups A and B before treatment*

Group variables	Group A	Group B	<i>p</i> [†]
Breast tenderness			0.20
Yes	42/88 (47.7)	52/91 (57.1)	
No	46/88 (52.3)	39/91 (42.9)	
Early tiredness			0.099
Yes	52/86 (60.5)	65/90 (72.2)	
No	34/86 (39.5)	25/90 (27.8)	
Appetite			0.370
Normal	8/88 (9.1)	10/87 (11.5)	
Less	72/88 (81.8)	67/87 (77.0)	
More	8/88 (9.1)	10/87 (11.5)	
Headache			0.665
Yes	33/88 (37.5)	37/91 (40.7)	
No	55/88 (62.5)	54/91 (59.3)	
Anxiety			0.805
Yes	61/86 (70.9)	63/91 (69.2)	
No	25/86 (29.1)	28/91 (30.8)	
Irritability			
Yes	69/86 (80.2)	80/91 (87.9)	
No	17/86 (19.8)	11/91 (12.1)	
Sleep pattern changes			0.579
Yes	48/86 (55.8)	47/91 (51.6)	
No	38/86 (44.2)	44/91 (48.4)	
Lack of energy			0.997
Yes	52/86 (60.5)	55/91 (60.4)	
No	34/86 (39.5)	36/91 (39.6)	
Depression and sadness			0.543
Yes	64/86 (74.4)	64/91 (70.3)	
No	22/86 (25.6)	27/91 (29.7)	

*Data are presented as n (%); †statistical significance assessed using the χ^2 test.

Table 2), but the reductions within each group were both significant ($p=0.002$ for Group A and $p=0.001$ for Group B). As for irritability, both placebo and calcium reduced the incidence of lack of energy in women with PMS.

Before intervention, the incidence of sadness and depression was similar in both groups (74.4% in Group A and 70.3% in Group B; Table 1). The McNemar test revealed a 17.4% reduction in Group A and a 37.1% reduction in Group B. The reduction in Group B was statistically significant ($p=0.0001$; Table 4).

Based on the results of the questionnaire, the average baseline scores for intensity of psychologic symptoms were 6.59 ± 3.60 in Group A and 7.26 ± 3.82 in Group B. After the study, the average scores were 5.85 ± 3.84 in Group A and 6.02 ± 3.68 in Group B. Using *t* test, the reduction of 16.3% in the average score in Group B was significant ($p=0.01$), while the reduction in symptoms in Group A was not significant ($p=0.16$).

Discussion

Similar studies have been performed by Thys-Jacobs et al [9] in 1989 using 33 cases, by Penland and Johnson [10] in 1993 with 10 cases, and by Bertone-Johnson et al [11] in 2005 with 1,968 cases. We performed a double-blind clinical trial involving 179 female college students. Comparison of the results before and after intervention revealed that depression and sadness were reduced significantly more in the women receiving calcium (27%) than in those receiving placebo (7%) ($p<0.002$). These results were similar to those from the study of Penland and Johnson [10]. They showed that calcium supplements alleviated concentration problems and affective and behavioral variations related to PMS ($p=0.01$). Thys-Jacobs [12] reported a 45% reduction in mood disorders and depressive symptoms in women receiving calcium supplements, compared with 28% in the placebo group. Bohrer and

Table 2. Frequency distribution of qualitative variables in Groups A and B after treatment*

Group variables	Group A	Group B	p^{\dagger}
Breast tenderness			0.42
Yes	45/88 (51.1)	52/91 (57.1)	
No	43/88 (48.9)	39/91 (42.9)	
Early tiredness			0.029 [‡]
Yes	45/86 (52.3)	32/89 (36.0)	
No	41/86 (47.7)	57/89 (64.0)	
Appetite			0.004 [‡]
Normal	11/88 (12.5)	15/91 (16.5)	
Less	66/88 (75.0)	48/91 (52.7)	
More	11/88 (12.5)	28/91 (30.8)	
Headache			0.66
Yes	33/88 (37.5)	37/91 (40.7)	
No	55/88 (62.5)	54/91 (59.3)	
Anxiety			0.62
Yes	59/86 (68.6)	58/89 (65.2)	
No	27/86 (31.4)	31/89 (34.8)	
Irritability			0.11
Yes	47/86 (54.7)	38/89 (42.7)	
No	39/86 (45.3)	51/89 (57.3)	
Sleep changes			0.99
Yes	40/85 (47.1)	50/90 (55.6)	
No	45/85 (52.9)	40/90 (44.4)	
Lack of energy			0.7
Yes	30/86 (34.9)	29/90 (32.2)	
No	56/86 (65.1)	61/90 (67.8)	
Depression and sadness			0.002 [‡]
Yes	58/86 (67.4)	39/89 (43.8)	
No	28/86 (32.6)	50/89 (56.2)	

*Data are presented as n (%); [†]statistical significance assessed using the χ^2 test; [‡]significant.

Table 3. Frequency distribution of early tiredness before and after treatment in Groups A and B*

Variables	Tiredness before treatment	Tiredness after treatment			p^{\dagger}
		No	Yes	Total	
Group A	No	15 (17.4)	19 (22.1)	34 (39.5)	0.37
	Yes	26 (30.2)	26 (30.2)	52 (60.5)	
Total		41 (47.7)	45 (52.3)	86 (100)	
Group B [‡]	No	19 (21.1)	6 (6.7)	25 (27.8)	0.001
	Yes	38 (42.2)	27 (30.0)	65 (72.2)	
Total		57 (63.3)	33 (36.7)	90 (100)	

*Data are presented as n (%); [†]statistical significance assessed using the McNemar test; [‡]of the respondents before treatment, one did not answer the question after treatment.

Krannich [13] found that calcium supplements effectively reduced depressive symptoms ($p=0.045$).

Overall, the results of these studies suggest that treatment with calcium supplements is an effective method for reducing mood disorders during PMS. However, calcium had no effect on the incidence of breast

tenderness in this study ($p=0.42$), which is in accordance with the results of the study by Penland and Johnson [10]. The incidence of tiredness was reduced ($p<0.001$), which was again in agreement with the results of Penland and Johnson [10] that showed a reduced incidence of early tiredness following calcium

Table 4. Frequency distribution of depression before and after treatment in Groups A and B*

Variables	Depression before treatment	Depression after treatment			p^{\dagger}
		No	Yes	Total	
Group A	No	13 (15.1)	9 (10.5)	22 (25.6)	0.30
	Yes	15 (17.4)	49 (57.0)	64 (74.4)	
Total		28 (32.6)	58 (67.4)	86 (100)	
Group B	No	17 (19.1)	9 (10.1)	26 (29.2)	0.0001
	Yes	33 (37.1)	30 (33.7)	63 (70.8)	
Total		50 (56.2)	39 (43.8)	89 (100)	

*Data are presented as n (%); †statistical significance assessed using the McNemar test.

supplementation ($p < 0.05$). Early tiredness and depression can be considered as two related symptoms, and any treatment that reduces depression will also cause improvements in early tiredness.

Both groups experienced improvements in appetite after treatment, but the improvement was greater in the calcium group ($p = 0.004$). Although the study of Alvir and Thys-Jacobs [14] demonstrated an apparent change in appetite disorders after administering calcium treatment for PMS symptoms, Lorenzen et al [15] failed to find any effect of calcium therapy on appetite disorders during PMS. Our findings suggest a possible relationship between mood disorders and appetite changes during PMS, but further studies are needed to confirm this hypothesis.

We found no significant effect of calcium therapy on headache, though Thys-Jacobs et al [2] and Penland and Johnson [10] found a positive effect of calcium treatment. This discrepancy may be due to differences in sample size. There was no improvements in anxiety in either group, but irritability was significantly reduced in both groups (both $p < 0.001$), suggesting that placebo, as well as calcium, also reduced irritability. However, the study by Thys-Jacobs et al [2] showed a 50% reduction in irritability symptoms after treatment with calcium compared with those who received placebo. The study of Thys-Jacobs in 2000 also revealed an effective improvement in mood disorders and irritability after treatment [12].

In this study, treatment had no significant effect on sleep disorders in Group A and Group B ($p = 0.74$ and 0.34 , respectively). In the study by Thys-Jacobs in 2000, however, there was a significant improvement in sleep disorders after treatment [12]. Again, this discrepancy may be due to differences in treatment duration, calcium dose or the number of cases. Larger studies are needed to clarify this relationship.

In a double-blind clinical trial involving 441 cases, improvements in physical and psychologic symptoms were observed in 48% of women who used calcium

supplements, compared with only 30% in the placebo group [2]. In the current study, a general improvement in physical and psychologic symptoms was observed in about 36% of patients receiving calcium, compared with only 29% receiving placebo.

An association between cyclic calcium changes and mood instability during each menstrual cycle has previously been reported in women with PMS [16]. An association between hypoparathyroidism and hypocalcemia as an aggravating factor in women with depressive symptoms has also been demonstrated [13]. Evidence for an association between secondary hyperparathyroidism and PMS symptoms, and for improvement of symptoms after calcium treatment shows the importance of calcium supplements [17]. Although there was a significant reduction in depressive symptoms after treatment, we did not measure serum calcium concentration and so were unable to prove this relationship.

In conclusion, the results of this study demonstrated that PMS symptoms of early tiredness, appetite changes, and depression were significantly improved by calcium treatment. This study, together with others [18–20], suggests that calcium therapy is a safe, effective and convenient method for reducing the intensity and frequency of PMS symptoms, with consequent improvements in quality of life.

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