Magnesium Supplementation Alleviates Premenstrual Symptoms of Fluid Retention

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ABSTRACT

We investigated the effect of a daily supplement of 200 mg of magnesium (as MgO) for two menstrual cycles on the severity of premenstrual symptoms in a randomized, double-blind, placebo-controlled, crossover study. A daily supplement of 200 mg of Mg (as MgO) or placebo was administered for two menstrual cycles to each volunteer, who kept a daily record of her symptoms, using a 4-point scale in a menstrual diary of 22 items. Symptoms were grouped into six categories: PMS-A (anxiety), PMS-C (craving), PMS-D (depression), PMS-H (hydration), PMS-O (other), and PMS-T (total overall symptoms). Urinary Mg output/24 hours was estimated from spot samples using the Mg/creatinine ratio. Analysis of variance for 38 women showed no effect of Mg supplementation compared with placebo in any category in the first month of supplementation. In the second month there was a greater reduction ($p = 0.009$) of symptoms of PMS-H (weight gain, swelling of extremities, breast tenderness, abdominal bloating) with Mg supplementation compared with placebo. Compliance to supplementation was confirmed by the greater mean estimated 24-hour urinary output of Mg ($p = 0.013$) during Mg supplementation (100.8 mg) compared with placebo (74.1 mg). A daily supplement of 200 mg of Mg (as MgO) reduced mild premenstrual symptoms of fluid retention in the second cycle of administration.

INTRODUCTION

THE PREMENSTRUAL SYNDROME (PMS) has been described by Reid and Yen as "the cyclic recurrence in the luteal phase of the menstrual cycle of a combination of distressing physical, psychological, and/or behavioral changes of sufficient severity to result in deterioration of interpersonal relationships and/or interference with normal activities."[1] The lack of consensus among gynecologists and researchers in defining PMS is due to the absence of measurable signs and the wide range of psychologic and somatic symptoms described for the condition. Abraham,[2] who has researched the dietary etiology of PMS for over two decades, has described four PMS categories: A (anxiety related), C (craving related), D (depression related), and H (hydration related). Although not universally accepted, this classification has found favor among several researchers.[3]

The prevalence of PMS among the female population varies greatly, according to reports. In London, Dalton[4] found that between 20% and 30% of women could be classified as sufferers, and others report even higher prevalence. For example, Johnson et al.[5] reported PMS in 87% of 996 nursing school graduates, whereas the incidence of PMS in 1395 gynecologic patients aged 13–54 years was 50% in another study.[6] These inconsistencies may partly reflect the lack of a clear definition of PMS as well as differences in study methodology, although they also depend on the group studied. Particular group bias includes age (peak incidence for women in their 30s has been reported[6]), parity, race, culture, occupation, lifestyle stresses,[7] and diet.

If subclasses of PMS exist, as suggested by Abraham,[2] there is the possibility of several distinct etiologies for the condition. Indeed, various hypotheses have been promulgated, involving interaction among ovarian steroid hormones, endogenous opioid peptide release in the brain, balance of central neurotransmitters, formation of inflammatory eicosanoids, and changes in peripheral autonomic and endocrine function. However, despite various investigations, the pathophysiologic basis of PMS still remains obscure, particularly in the absence of animal models for the condition. Although the ovarian hormone imbalance hypothesis finds most favor and progesterone administration in the latter half of the cycle continues to be first-line treatment by general practitioners,[8] there are still many uncertainties about its validity.[9]

Various reports, many of a preliminary nature or based on clinical experience, suggest that women suffering from PMS consume more refined carbohydrate and dairy products and less vitamin B-complex, iron, zinc, and magnesium (Mg) than nonsufferers.[10] Of all the dietary factors suggested, magnesium is the best researched. Mg is low in the diets of a substantial proportion of women consuming western-type diets, as has been demonstrated in many dietary surveys. For example, the mean intake of Mg of over 1000 British women was 237 mg/day,[11] corresponding to 88% of the Reference Nutrient Intake (RNI).[12]

The role of Mg deficiency in the etiology of PMS was first proposed by Abraham,[2] who reasoned that in Mg deficiency, enhanced intake of Mg would have a sedative effect on neuromuscular excitability and restore cell membrane electrolyte imbalance to normal, which would have a diverse subtle physiologic effect. As Mg is found predominantly inside the cell, intracellular Mg concentration is a better reflection of body status than blood measurements. Thus, although plasma Mg levels have been reported to be unrelated to PMS,[13] poor erythrocyte Mg status is the most consistent physiologic abnormality found among PMS sufferers compared with normal controls.[14–16]

Apart from the role that Mg plays in maintenance of the electrical potential of the cell membrane, including neuromuscular function, it is an essential cofactor for enzymes that require ATP. It is also involved in the synthesis and replication of RNA and DNA.[17] Hence, Mg deficiency is likely to affect the normal functioning of many body systems, including liver function.[18] Of particular relevance to the multifaceted presentations of PMS is the role of Mg in stimulating the synthesis of nitric oxide (NO)[19] and eicosanoids[20] involved in balancing the inflammatory response, as well as its role in neurotransmitter activity.[21]

The only controlled study carried out on Mg supplementation alone for its effects on PMS was that of Facchinetti et al.[3] These authors found that 360 mg of Mg per day given in three divided doses in the luteal phase of the cycle alleviated anxiety-related PMS (mood changes), compared with placebo, when administered over four menstrual cycles. The same authors found that a similar regimen was effective in treating premenstrual migraine headaches.[22]

The present study was inspired by the work of Facchinetti et al.[3] However, our protocol differed from that used by the Italian workers in that (1) the supplement (or placebo) was administered throughout the menstrual cycle and not just during the latter half of it, (2) the amount of Mg administered per day was lower (200 mg/day rather than 360 mg/day), and (3) the Mg supplement was given in one single daily dose rather than in three divided doses throughout the day. The low dose of Mg was chosen to represent a true supplement to dietary intake rather than being a pharmacologic dose.

MATERIALS AND METHODS

Ethical permission

The protocol for the study was scrutinized and allowed by The University of Reading Ethics and Research Committee.

Volunteers

Women suffering from premenstrual symptoms were recruited from among the student and employee population of The University of Reading by means of poster advertisements placed throughout the university. A signed consent from each volunteer and agreement from the volunteer's general practitioner were required before entry into the study.

Experimental design

The duration of dietary supplementation was four menstrual cycles. The volunteers were divided randomly into two groups. For the first two cycles, starting at day 1 of the menstrual cycle (the first day of bleeding), members of one group each received a single Mg tablet per day, and each member of the other group received one placebo tablet per day. At the start of the third menstrual cycle, the daily supplement was crossed over for each volunteer, so that those taking Mg were requested to take placebo, and vice versa, and to continue to do so to the end of the fourth cycle.

The formulation of the Mg supplement was 200 mg magnesium oxide (MgO) (heavy precipitate) with 100 mg of mixed amino acids (Lamberts Healthcare Ltd., Tunbridge Wells, Kent, U.K.). The placebo tablets contained microcrystalline cellulose. All tablets were supplied in coded, sealed, plastic containers sufficient for 1 month for one volunteer. Each month's supply of tablets were sent by post or delivered by hand with instructions for use and a blank menstrual diary to be filled in from the start of the next cycle.

Premenstrual symptom records

Before the study commenced, volunteers were asked to complete a Menstrual Health Questionnaire (MHQ), modified from Warner and Bancroft.[7] This was divided into two parts involving (1) questions on the volunteer's general menstrual health, age, parity, oral contraceptive (OC) use, and premenstrual symptom experience and (2) a retrospective assessment of the severity of symptoms suffered during the last cycle, using a 27-symptom classification, each to be assessed on a 5-point scale (1, very mild; 2, mild; 3, moderate; 4, severe; 5, very severe) for the premenstrual and postmenstrual phases of the cycle. Only those subjects showing at least a 30% drop in total symptoms between premen-

strual and postmenstrual scores were entered into the study.

Once supplementation had started, volunteers were asked to keep a daily record of their symptoms in a 22-item menstrual diary (MD) based on the Moos[23] questionnaire, using a 4-point scale (0, none; 1, mild—present but does not interfere with activities; 2, moderate—present and interferes with activities but not disabling; 3, severe—disabling, unable to function).

Collection and analysis of urine

Each volunteer was asked to supply three spot urine samples, one before the onset of the study (baseline) and one each while taking the first and second supplements. Urine samples during the supplementation phase were taken after 3 weeks of treatment to ensure a steady flux of Mg. No guidelines were given about the time of day to take urine samples, although volunteers were asked to pack the samples quickly after collection, according to a protocol, and send them immediately by first class mail to the pathology laboratory of the Royal Berkshire Hospital, Reading, where they were stored frozen before analysis.

Urine samples were diluted appropriately and analyzed for creatinine and Mg by the appropriate Kodak Ektachem Clinical Chemistry Slide (Clinical Products Division, Eastman Kodak Company, Rochester, NY). Estimated 24-hour urinary output of Mg was calculated without correction for body weight on the assumption that each woman had an output of 8.752 mmol (990 mg) of creatinine per day.[24]

Statistical analysis

Table 1 shows how the 27 symptoms recorded in the MHQ were classified for data handling. The classification was a modification of that of Abraham,[2] using six categories: PMS-A (anxiety), PMS-C (craving), PMS-D (depression), PMS-H (hydration), PMS-O (other), and PMS-T (total). The 22 symptoms of the MD were classified in a similar way (Table 2) for each menstrual cycle. A premenstrual score was calculated for each of these categories by summing the scores within a category for the 7 days before the onset of menses.

Data were collated using DataEase 4.0 (Saphire DataEase Ltd, Ilford, Essex, U.K.) and analyzed using SAS 6.04 (Statistical Analysis System, SAS, Institute Inc., Cary, NC). Data sets for 1 month of treatment (cycles 1 + 3) and for 2

TABLE 1. CLASSIFICATION OF 27 SYMPTOMS OF MENSTRUAL HEALTH
QUESTIONNAIRE SCORED RETROSPECTIVELY ON 5-POINT SCALE

Symptom category	Maximum score	Symptoms
PMS-A (anxiety)	25	Difficulty in sleeping, feeling tense, irritable, clumsiness (dropping things), mood swings
PMS-C (craving)	20	Headache, craving for sweet foods, craving for salty food, craving for other type of food
PMS-D (depression)	30	Feeling depressed, getting angry for no reason, easily upset, poor concentration or memory, feeling bad about myself, violent feelings
PMS-H (hydration)	10	Bloated feeling in the abdomen, tender breasts
PMS-O (other)	50	Change in bowel habit, period-type pains, backache, passing water frequently, general aches/ pains, infections (e.g., colds), allergic reactions, hot flushes or cold sweats, nausea/ sickness, spots (e.g., acne)
Total	135	Sum of the overall symptoms

months of treatment (cycles 2 + 4) were subjected to analysis of variance (ANOVA).

The estimated 24-hour urinary Mg output during Mg supplementation treatment was compared with output while on placebo treatment, using ANOVA, with baseline values as covariate.

RESULTS

Of the 54 volunteers who completed the MHQ, 41 completed the MD for cycle 1, 38 for cycle 2, 30 for cycle 3, and 24 for cycle 4. In order not to break promised volunteer confidentiality, the reasons for dropout were not followed up. The total numbers of urine specimens received and analyzed were 50 at baseline, 45 during menstrual cycles 1 and 2, and 40 during menstrual cycles 3 and 4. Thirty-seven volunteers provided all three urine samples required for the study.

Menstrual Health Questionnaire (MHQ)

Responses to the MHQ were analyzed for the 38 volunteers who provided complete data for menstrual cycle 2. Only data on these 38 volunteers were included in the ANOVA of the effect of Mg versus placebo on PMS symptoms. The age range of the 38 subjects was 18–50 years, but the majority (71%) were in the age group 18–25 years old. The other age range groups were 26–34 years (7.9%), 35–41 years (13.2%), and 41–50 years (7.9%).

The majority (65.7%) of volunteers had been between 12 and 13 years of age at menarche, 13.1% had been <12 years old, and 21.1% had been >13 years old. A total of 71.1% of the volunteers reported regular menstruation, with their periods starting within 2–3 days of the predicted date each month, 26.3% reported starting within 4–10 days of the predicted date, and only 2.6% reported their period starting within >10 days of

TABLE 2. CLASSIFICATION OF 22 SYMPTOMS IN MENSTRUAL DIARY SCORED DAILY ON 4-POINT SCALE

Symptom category	Maximum premenstrual score	Symptoms
PMS-A (anxiety)	84	Nervous tension, mood swings, irritability, anxiety
PMS-C (craving)	126	Headache, craving for sweets, increased appetite, heart pounding, fatigue, dizziness or faintness
PMS-D (depression)	105	Depression, forgetfulness, crying, confusion, insomnia
PMS-H (hydration)	84	Weight gain, swelling of extremities, breast tenderness, abdominal bloating
PMS-O (other)	63	Cramps (low abdominal), backaches, general aches/pains
Total	462	Sum of the overall symptoms

the predicted date each month. Menstruation lasting 5 days was reported by 57.9% of the subjects, <5 days by 13.2%, and >5 days by 28.9% of the subjects. Menstruation was described as medium blood loss by 70.3%, light blood loss by 13.5%, and heavy blood loss by 16.2%.

With reference to parity, 7 of the 38 volunteers (18.4%) had given birth to one or more children. OC were taken by 31.6% of the 38 women, of whom 50% were in their first year of OC treatment, and 33.3% had been taking OC for the last 2–3 years. Within the group not taking OC ($n = 26$), 2 subjects reported that they had stopped taking OC less than 1 year ago, and 6 subjects reported that they had stopped taking OC longer than 1 year ago.

When asked if they felt that they were currently subject to stress, 81.1% reported some stress, 5.4% reported a great deal of stress, and 13.5% reported no stress. Regarding their last menstrual period (on which they were also required to made a retrospective assessment score of the severity of PMS suffered, using a 27 PMS symptom classification), 59.5% selected the alternative "as bad as usual," 13.5% selected "better than usual," 10.8% selected "worse than usual," and 16.2% selected the alternative "no unpleasant changes."

Of the 38 women, 26 reported suffering from PMS for 1–5 years, 6 for 6–10 years, and 4 for >10 years (2 did not report). When asked if they have found any cure for PMS, 77.8% had not, but 22.2% had found a variety of remedies, including exercise, relaxation, and taking evening primrose oil.

The second part (Part II) of the MHQ yielded data on the symptom scores in the premenstrual and postmenstrual phases of the volunteers' last cycle. Mean premenstrual scores and the difference between mean premenstrual and postmen-

strual scores for each of the PMS categories are shown in Table 3.

Premenstrual symptoms

The mean PMS scores for Mg or placebo supplementation for pooled arms of the study at 1 and 2 months are shown in Table 4. The percentage of maximum scores for 1 and 2 months of supplementation was low, varying between 5.8 and 16.5 for all symptoms, indicating that most of the volunteers were suffering only mild symptoms during the 7 days included in the score. Indeed, category PMS-O, comprising symptoms not necessarily associated with PMS, was the most prevalent category (14% of maximum score). This was followed by PMS-A, PMS-C, PMS-H, and PMS-D (12%, 8.9%, 7.4%, and 6.9% of maximum score, respectively).

ANOVA showed no significant difference in any of the symptom categories after 1 month of supplementation. However, after 2 months of supplementation, a significant difference ($p = 0.009$) was found between mean premenstrual scores for Mg (4.96) and placebo (7.19) supplementation for PMS-H (Table 4), although 2 months of supplementation showed no significant effect of the different treatments for any other symptom category, including PMS-T scores, even though scores were all lower when the subjects were taking Mg. Tests for the carryover effect of Mg supplementation in the first arm of the study into the placebo period of the second arm of the study were nonsignificant.

Urinary magnesium output

A total of 37 subjects provided all three urine samples required in the study, and these were in-

TABLE 3. PREMENSTRUAL SYMPTOM CATEGORIES FROM THE MENSTRUAL HEALTH QUESTIONNAIRE:
COMPARISON OF MEAN PREMENSTRUAL AND POSTMENSTRUAL SCORES FOR 38 WOMEN

Symptom category	Premenstrual scores[a]	Postmenstrual scores[a]	Difference between premenstrual and postmenstrual scores[a]
PMS-A (anxiety)	19.11 ± 5.38	3.79 ± 4.10	15.32 ± 6.63
PMS-C (craving)	5.50 ± 3.11	1.53 ± 1.81	3.97 ± 3.31
PMS-D (depression)	9.84 ± 3.81	2.02 ± 2.24	7.82 ± 4.18
PMS-H (hydration	4.47 ± 2.45	0.68 ± 0.96	3.79 ± 2.42
PMS-O (other)	12.95 ± 6.84	3.37 ± 3.91	9.58 ± 6.36
Total	51.87 ± 14.77	11.38 ± 11.52	40.47 ± 16.90

[a]Mean ± SD.

TABLE 4.   PREMENSTRUAL SYMPTOM SCORES FROM MENSTRUAL DIARIES
FOR WOMEN RECEIVING DAILY SUPPLEMENT OF MG OR PLACEBO

Months of supplementation	Symptom category	Mg		Placebo	
		n	Score[a]	n	Score[a]
1	PMS-A	35	10.74 ± 7.81	36	10.08 ± 7.47
	PMS-C		10.77 ± 7.19		13.19 ± 9.45
	PMS-D		7.89 ± 6.47		8.28 ± 7.70
	PMS-H		6.09 ± 3.85		6.56 ± 4.88
	PMS-O		8.80 ± 7.27		9.97 ± 9.74
	Total		44.29 ± 26.12		48.05 ± 34.15
2	PMS-A	30	8.30 ± 8.11	32	12.43 ± 11.93
	PMS-C		9.90 ± 8.46		11.46 ± 7.21
	PMS-D		6.13 ± 4.43		7.34 ± 7.08
	PMS-H*		4.96 ± 3.09		7.19 ± 5.08
	PMS-O		7.53 ± 8.21		10.40 ± 10.49
	Total		36.80 ± 23.88		48.75 ± 35.25

[a]Mean ± SD.
*Significantly different from placebo ($p = 0.009$).

cluded in the ANOVA. The estimated 24-hour urinary Mg output of these samples is shown as distribution plots in Figure 1 and as mean data for the 37 subjects at baseline and during supplementation in Table 5. ANOVA, using baseline data (mean of 71.6 mg/day) as covariate, showed that mean estimated 24-hour urinary Mg output significantly increased ($p = 0.013$) when subjects were taking Mg supplement (mean of 100.8 mg/day) compared with placebo (mean of 74.1 mg/day).

DISCUSSION

The majority of the volunteers (72%) were university students, aged 18–25 years old, who suffered only mild premenstrual symptoms that were not severe enough to be classified as PMS. In this age group, the incidence of premenstrual symptomatology tends to be lower than in older age groups.[7,25,26] Stressful life events have been postulated to exacerbate the symptoms. Indeed, stress load must be a factor to consider when recruiting volunteers.[7,27] However, only 5.4% of our subjects recorded undergoing a great deal of stress at the time the MHQ was completed, so stress may not have been a major factor for women in this study.

OC users were not excluded from this study. Although controversial, clinical experience indicates that OC may help to relieve premenstrual symptoms at least in the short term, and, thus, OC users are less likely to suffer. Chronic use of

OC, however, has been related to the development of depression and other PMS symptoms, such as breast tenderness due to estrogen dominance.[28] In the present study, most volunteers using OC ($n = 12$) had been taking them for less than a year, and in view of this fact and the small numbers involved, separate analysis of this subset was not attempted.

Compared with maximum scores, the MHQ symptom scores showed PMS-A as being most prevalent among the 38 volunteers (76%). PMS-H was the next most prevalent symptom category (48% of maximum score), with the other PMS categories ranging from 24% to 38% of the maximum scores. The finding that PMS-A was the predominant category coincides with Abra-
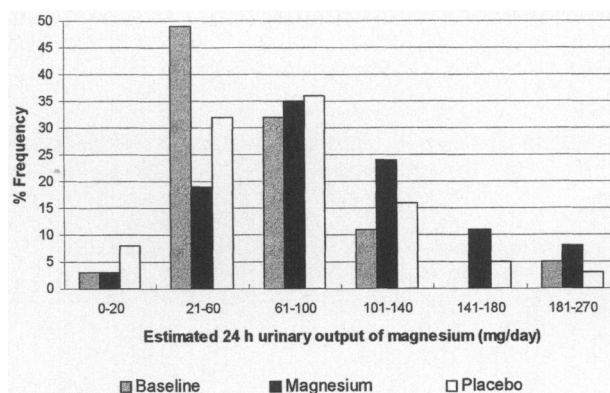

FIG. 1.   Distribution of estimated 24-hour urinary output of Mg (mg/day) of 37 women at baseline (no supplementation) and during supplementation with 200 mg/day Mg or placebo.

Urine samples	Means (mg/day)	SD
Baseline	71.6	45.4
Magnesium	100.8*	51.1
Placebo	74.1	42.3

*Significantly different from placebo (p = 0.013).

ham and Rumley's clinical and experimental findings.[29]

The premenstrual scores and the difference between premenstrual and postmenstrual scores for each of the symptom categories from the MHQ (Table 3) show little variation, indicating that the symptoms suffered in the postmenstrual phase were slight. Thus, those recorded in the premenstrual phase can truly be regarded as part of the premenstrual syndrome. These results concur with a proposed definition of premenstrual syndrome by O'Brien[30] that symptoms in the luteal phase of the cycle are relieved by the onset of menstruation or during menstruation, with a symptom-free follicular phase postmenstruation.

Premenstrual scores from the MD for the various symptom categories showed Mg supplementation (200 mg/day) to be helpful (p = 0.009) in alleviating symptoms of PMS-H compared with placebo after 2 months but not after 1 month of treatment (Table 4). No differences between Mg and placebo treatment were observed for any other premenstrual score categories, although all scores were lower under Mg supplementation than placebo after 2 months' supplementation. As baseline MD were not requested in this study, the extent of the placebo effect was not determined, although other studies on intervention treatment for PMS have shown that the placebo effect is substantial.[31,32]

Although all symptom categories showed reduction of symptoms after 2 months of Mg supplementation compared with placebo, confirming the findings of Facchinetti et al.,[3] the categories showing a statistically significant change were different in the two studies. Facchinetti et al.[3] showed a significant difference in negative affect (equivalent to the category of PMS-D in this report) and PMS-T symptoms but not of symptoms of PMS-H. Differences in the study design may be partly responsible for this. Facchinetti et al.[3] administered the Mg supplement from day 15 to

the end of the cycle, not continuously, and the dose was higher (360 mg Mg/day) and administered in three divided doses. Also, the group of women randomized to take an Mg supplement for 2 months was continued on Mg for a further 2 months. At the end of that time, the researchers were able to show a significant effect of Mg supplementation compared with 2 months of Mg supplementation in symptoms of PMS-H.

It is not clear why PMS-H should be the category to show response in our study after only 2 months of Mg supplementation, although the state of Mg repletion of the subjects may have been different. Mg repletion is best assessed through urinary Mg output, which was not measured by Facchinetti et al.[3] Our results showed mean estimated Mg output to be at the lower end of the normal range.

The lack of significant effects of treatment in the first month of supplementation (Table 4) in our study may have been due to the low dose used for Mg supplementation (200 mg/day), which may have required several weeks to normalize low Mg status. This likelihood raises the question of a carryover effect. No washout period was allowed between treatments in this study, so it is possible that symptoms experienced among the placebo treatment group in the second arm of the study may have been influenced even by the nonsignificant effect of carryover of Mg supplementation from the first arm of the study. Hence, if a washout period had been planned as part of the protocol, it is likely that further significance in the differences between the groups would have been found.

The mean value of 71.6 mg/day (Table 5) for the estimated 24-hour urinary output of Mg at baseline for the 37 women completing the urine collections was below the normal range of 72.9–109.4 mg/24 hours.[33] A low output of Mg is a reflection of a low dietary intake, which is common among women in Britain. Compared with the RNI for Mg for adult women of 270 mg/day,[12] Gregory et al.[11] showed, from a weighed dietary survey of over 1000 women, that the mean intake of Mg for all ages was 237 mg/day. The intake was even lower in 16–24-year-old women (mean of 215 mg/day), and for women with the lowest intake (2.5% of all women surveyed), it was less than 105 mg/day.

Support for these findings of low Mg intake among British women also comes from the British National Food Survey,[34] in which the mean daily

Mg intake estimated for women was only 84% of the RNI. Volunteers in the present study were mostly young female students, who may not have the time or the inclination to include sufficient whole grain cereals, nuts, beans, and dark green leafy vegetables in their diets to obtain an adequate intake of Mg.

The mean estimated 24-hour urinary output of Mg for 37 subjects while on placebo treatment was not significantly different from baseline values (Table 5), indicating that placebo had no influence on Mg output, as might be expected. When the subjects were supplemented with Mg, however, there was a significant increase in Mg output in the urine ($p = 0.013$). Although significant, the increased value (mean 100.8 mg/day) was still within the normal range, although at the higher end of the range. Although the extent of absorption of Mg from MgO by human subjects is unknown, this form of the mineral has been favored for use in dietary supplements because of its low bulk. This study shows that a supplement providing 200 mg/day of elemental Mg as MgO can increase urinary Mg output, indicating its bioavailability.

CONCLUSIONS

A low-dose daily supplement of 200 mg of MgO significantly reduced mild premenstrual symptoms of fluid retention (PMS-H) in women suffering premenstrual symptoms in the second cycle of supplementation, but not during the first cycle, compared with placebo. Compliance to treatment was confirmed by a significant increase in urinary Mg excretion while women were supplemented with MgO. Further studies are warranted on Mg supplementation of subjects with more severe symptoms, using higher doses of Mg, and making adequate allowance for a carry-over effect.

ACKNOWLEDGMENTS

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