

Background

Premenstrual syndrome (PMS) has been described as one of the most common disorders in females, afflicting millions of premenopausal women. As many as 30-50% of women experience symptoms of PMS, and approximately 5% report their symptoms to be severe enough to have a substantial impact on their physical and social health (1). 10% of women who experience PMS are so severely affected that they miss one to three days of school or work every month (2).

PMS is characterized by rapid changes in mood (e.g. depression, irritability, mood swings, anger, aggression, crying spells, tension, anxiety) and physical symptoms (e.g. abdominal discomfort, breast tenderness, headache, generalized pain, bloating, edema, fatigue, insomnia) during the late luteal phase of the menstrual cycle (1). These symptoms remit soon after the onset of menses.

Calcium has been associated with PMS and modulation of affect in several ways. First, disturbances in calcium and affective disorders have been proposed for fifty years. Second, the link between estrogen and calcium levels has also been long established. Finally, more recent studies have found calcium supplementation to significantly reduce the symptoms of PMS.

Unfortunately, the theories that have been proposed to explain the link between calcium and PMS are problematic in that they often do not fully explain the results of these studies. Thus far, the only real consensus has been the association of calcium dysregulation and decreased calcium supply in women who suffer from PMS. Moreover, it remains unclear why decreased calcium associated with estrogen surges during the midcycle and early luteal phases would result in acute symptoms during the late luteal phase. In this paper, I will first review the various studies linking calcium and affectivity, calcium and the menstrual cycle, and calcium supplementation and PMS. I will then describe and probe the theories that have been proposed, and present an alternative theory of the association between calcium and PMS.

Calcium and Affective Disorders

Calcium plays a major role in neuronal signaling in the central nervous system. The amount of intracellular and extracellular calcium determines, in large part, the amount of neurotransmitter release from the pre-synaptic neuron. Post-synaptically, calcium entry can precipitate biochemical cascades that regulate protein activity. Thus, it is logical that disturbances in calcium balance can result in neurological symptoms.

Hypercalcemia and Affect. Hypercalcemia has been associated with depression (3). In hyperparathyroidism, which increases parathyroid hormone (PTH) levels and calcium resorption from bone, and thus serum calcium levels, symptoms include anxiety, mild personality changes, confusion, and depression—symptoms also associated with PMS (4). Treatment with parathyroid surgery has been reported to alleviate symptoms of fatigability, difficulty concentrating, tension, sadness, and failing memory (5). A recent study by Joborn et al. examining monoamine metabolite levels in hyperparathyroidism found that patients with primary hyperparathyroidism had low concentrations of monoamine metabolites in their cerebral spinal fluid. Following parathyroid surgery, they observed an improvement in the patients' psychiatric symptoms with an increase in the monoamine metabolites (6). These results corroborate the "Monoamine Theory of Affect," as well as support the significance of calcium's role in maintaining proper CNS function. The sum of these observations suggests that dysregulation of calcium levels, due to hyperparathyroidism, may result in negative affective symptoms, and that this mechanism may be mediated by abnormal monoamine metabolism.

Hypocalcemia and PMS. Hypocalcemia has been associated with irritability, anxiety, and mania, symptoms often associated with PMS. Thys-Jacobs et al. compared calcium-regulating hormones and calcium levels across the menstrual cycle in women with PMS and normals. They found significantly lower levels of calcium in women who suffered PMS, as well as a 30% increase in PTH at the midcycle estradiol peak, corresponding to a decrease in calcium. They explained this seemingly paradoxical situation (increased PTH should cause increased calcium levels) by suggesting that the increase in PTH was to compensate for the drop in calcium levels. This increase in PTH was found only in women with PMS because they had a lower baseline calcium supply to begin with, and thus, a drop in calcium due to increased estradiol during

the midcycle would cause calcium levels to dip lower than normal and induce increased PTH production to counter this drop. In normal subjects, the drop in calcium due to increased estradiol was not significant enough to induce PTH compensation. In other words, the patients with PMS exhibited midcycle elevations of PTH and a transient secondary hyperparathyroidism to compensate for abnormally low levels of calcium during the estradiol peak (7). The problem with this explanation is that it contradicts the previous findings described above linking hypercalcemia and affective disorders. How can these opposite states result in the same symptomatology?

Another confounding factor regards the results of a previous study that examined serum concentrations of sex hormones (estrogen, progesterone, and testosterone) and calcium and magnesium levels in ten healthy females. They found a significant increase in the ratio of Ca^{2+}/Mg^{2+} during the ovulatory and luteal phases, corresponding to increases in estrogen during these periods. The authors concluded that Mg^{2+} deficiency or an increased Ca^{2+}/Mg^{2+} ratio may alter synaptic transmission and lead to the symptoms of PMS (8). This opposes the claim from the Thys-Jacobs et al. study cited above that decreased Ca^{2+} results in the symptoms of PMS. A problem with both studies was the small sample size (twelve subjects in the Thys Jacobs study and ten subjects in this study).

In spite of these difficulties, other studies exist in support of the association of hypocalcemia and PMS. In one retrospective study comparing women with confirmed vertebral osteoporosis and controls, researchers found a higher risk of osteoporosis in women with a history of PMS (9). Another study showed decreased bone mass in women who suffered from PMS versus controls (10). These results have even lead to the suggestion that PMS may be a marker for low calcium status and may serve as a warning sign of increased risk of osteoporosis to pre-menopausal women (11).

Estrogen and Calcium

Estrogen is believed to decrease serum calcium levels by enhancing calcium deposition in bone and suppressing bone resorption. Estrogen regulates intestinal absorption of calcium and decreases expression of parathyroid hormone. Much of the research on the relationship between estrogen and calcium has come from studying post-menopausal women and the effects of estrogen decline during that period. For example, PTH was found to increase after menopause 12, and osteoporosis has long been associated with estrogen decline following menopause (13). Though these studies are quite dated, their findings have been maintained.

Calcium supplementation and PMS

There have been only three studies published in the past decade examining the efficacy of calcium supplementation in alleviating PMS symptomatology. The first study published in 1989 analyzed the effects of calcium supplementation in 33 women. Half of the women were placed on calcium supplementation for 3 months, and then switched over to placebo for 3 months. The other half were placed on placebo for 3 months and then switched over to calcium supplements for 3 months. This was a randomized, double-blind, crossover, placebo-controlled study. They found that calcium reduced symptoms during the luteal and menstrual phases. Supplementation significantly reduced negative affect, water retention, and pain in the premenstrual and menstrual phases (14).

An exploratory study was undertaken by Penland and Johnson in 1993. For 4 30-day dietary periods, they tested the effects of calcium and manganese intake on 47 PMS symptoms in 10 healthy women. They discovered that calcium and manganese intake improved mood, concentration, and behavior symptoms in general, reduced pain in the menstrual phase, and reduced water retention during the premenstrual phase (15).

The most recent study conducted in 1998 was a prospective, randomized, double-blind, placebo-controlled, parallel-group, multicenter clinical trial. 441 women who met inclusion criteria were evaluated for changes in PMS symptom factors over the course of three months of daily supplementation with 1200 mg of elemental calcium. Subjects completed a PMS Diary every night to record how they felt over the previous 24 hour period. Their results showed significantly lower symptom scores in the second and third months of

treatment. By the third calcium-treated cycle, supplementation resulted in a 48% overall reduction in total symptom scores, compared to a 30% reduction in placebo (16). While this 48% reduction is certainly significant, the 30% reduction in placebo is interesting to note as well. Is it possible that keeping a PMS Diary could have alleviated symptoms by making women more aware, and consequently, more in control of their affect and behavior? Could this have played a role in decreasing symptoms in both control and experimental groups? Could this effect also be used as a therapeutic tool for women who suffer from PMS?

The conclusion that can be drawn from these studies is that calcium can be used as a safe and effective treatment for PMS. The results further support the hypothesis that negative affectivity in PMS is due to a basal state of hypocalcemia.

An Integrative Theory of calcium and PMS

Despite all these studies, it is still not absolutely clear whether hypocalcemia or hypercalcemia leads to PMS. As mentioned earlier, symptoms of hyperparathyroidism are incredibly similar to the affective symptoms of PMS. On the other hand there is a large body of evidence that suggests that PMS is due to hypocalcemia, perhaps the most persuasive of which is the alleviation of PMS symptoms with calcium supplementation. The connection between sex hormones and calcium levels has been proposed by Thys-Jacobs. Her explanation is that women who suffer from PMS have a reduced calcium supply. When estrogen increases during midcycle and the luteal phase, serum calcium levels drop to abnormally low levels. This causes a compensatory increase in PTH, which was observed in one of her studies (7). The presence of this increased PTH during estrogen surge confirms reduced calcium status in women with PMS. Hence, PMS is linked to hypocalcemia.

In this paper, I would like to expand this hypothesis further to incorporate the relationship between hypercalcemia and affect in order to better explain the time course of the onset of symptoms and changes in estrogen. This is necessary because the increases in estrogen, and consequent decreases in serum calcium, occur first at midcycle (day 14, or two weeks before menses) and the luteal phase (peaking at about one week before menses). How do we account for the fact that PMS symptoms actually occur within the last week of the cycle, when estrogen levels are dropping again and calcium levels are presumably rising? Here is the theory I propose. Women who suffer PMS indeed have a lower baseline calcium status. Thus, when estrogen increases, calcium drops to below normal and PTH production increases, as Thys-Jacobs has proposed. However, PTH has long-lasting effects. Thus, when estrogen levels drop just before menses, calcium levels subsequently rise, but because PTH levels are still elevated, calcium levels rise even more than would be expected from the effects of decreased estrogen alone. In other words, calcium levels do not just drop below normal during the estrogen rise, but they also increase more than normal during the estrogen fall due to the presence of PTH. Thus, while the underlying problem is decreased calcium supply, the causal mechanism of PMS symptomatology is increased relative amplitudes of fluctuation of calcium levels over the course of the menstrual cycle, particularly in the luteal and pre-menses phases. This may explain why the efficacy of calcium supplementation increases over time. Not only does supplementation increase baseline calcium status, but it may also decrease PTH response to decreased calcium, preventing excessive increases in calcium just before menses.

Conclusion

Evidence supports the role of both hypercalcemia and hypocalcemia in affective disorders. In the context of PMS, there has been greater evidence to support the theory that PMS is associated with low calcium supply. However, the actual mechanism of disturbed affect may involve more than just decreased calcium levels. Instead, I propose in this paper that it is the greater fluctuation in calcium levels, due to an underlying hypocalcemic state, that leads to the symptoms observed in PMS. This theory better accounts for the timing of the onset of PMS symptoms with calcium fluctuations. Furthermore, the theory may better explain why the ameliorative effects of calcium supplementation are not significant until two to three months of supplementation. That is, calcium supplementation may work not only by increasing calcium supply, but also by re-stabilizing the calcium homeostatic system as a whole.

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