Review Article

The molecular mechanisms of Vitamin D effects on alleviating premenstrual syndrome pain

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Abstract

Premenstrual syndrome (PMS) is a hormone dependent pathophysiologic state with known somatic and affective symptoms. Vitamin D3 as a secosteroid hormone has different effects on several disorders. In this review, we declared some potential benefits of vitamin D3 regarding the alleviation of PMS symptoms; also, we have reported the results of the literature review about vitamin D and PMS.

Keywords: Vitamin D, Premenstrual syndrome, Pain

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Introduction

Premenstrual syndrome (PMS)

PMS is a hormone dependent pathophysiologic state. Physical and behavioral symptoms are appeared after ovulation and they seem to be progesterone dependent (1, 2). Although the pathophysiology of all PMS symptoms are not clarified up to now, bilateral interaction between sex hormones and neurotransmitters could explain some of these symptoms.

Vitamin D3

VD3 is a secosteroid hormone with well-known musculoskeletal and extra-skeletal effects in several tissues (3). Although there are a number of studies that indicate the relation between low levels of vitamin D and pain syndromes (4, 5), the causative association was not shown till now.

This review is arranged in three parts. First it is focused on proposed cellular and molecular mechanisms of pain as one of the major manifestations of PMS, then the published literature in pubmed about the vitamin D and PMS were discussed and at the last section the hypothesis regarding the possible effects of vitamin D3 on pain reducing in PMS cases were accounted.

Potential cellular and molecular mechanisms of PMS symptoms

Among the most common complications of PMS are abdominal cramps and headache.

The underlying mechanism of pain in PMS is not fully understood. One of the pathophysiologic interpretations of the pain in PMS is related to progesterone metabolites (6). Although the symptoms of PMS are initiated in luteal phase of menstruation cycle, which is concurrent with progesterone release by corpus luteum (7), It seems that progesterone levels are not different between PMS and non PMS women (8) and it could not per se be the etiology of PMS syndromes (9).

The pattern of progesterone changes during menstrual cycles has important role in symptom creation of PMS cases. A recent study also showed that

Table 1: Articles investigated the effects of vitamin D supplementation in PMS cases.

Article's title	Year	Study design	Dose and duration of vitamin D prescription	Outcomes
Vitamin D supplementation for premenstrual syndrome-related mood disorders in adolescents with severe hypovitaminosis D (35)	2016	Randomized clinical trial (15-21 years old women with severe PMS affective symptoms and hypo-vitaminosis D)	200,000 IU vitamin D at first, followed by 25,000 IU (every 2 weeks) for a 4-month period	The severity of affective symptoms were decreased with vitamin D intake in treatment group No effect on nausea and constipation was seen
Calcium versus oral contraceptive pills containing drospirenone for the treatment of mild to moderate premenstrual syndrome: a double blind randomized placebo controlled trial (36)	2016	Double-blind randomized placebo controlled trial, mild to moderate premenstrual syndrome	Three groups, 1: combined OCP, 2: vitamin D/Ca (400 IU/(400 mg), 3: placebo Prescription of drugs started from 3rd day of menstruation up to 2 days for 3 months	The proportion of women with improved symptoms increased in groups 1 and 2 compared to 3 Severity of PMS problems decreased in groups 1 and 2 compared to 3
Evaluating the effects of vitamin D and vitamin E supplement on premenstrual syndrome: A randomized, double-blind, controlled trial (37)	2016	Double-blind randomized controlled trial (15-45 years old women with known PMS)	Three groups, 1: vitamin D (200mg/ day), 2: vitamin E (100mg/day), 3: placebo (one/day) supplementation was provided from the first to the last day of menstruation cycle for 2 months	Mean PMS scores of all three groups were decreased after intervention There was not any significant difference between three groups
Effect of treatment with dydrogesterone or calcium plus vitamin D on the severity of premenstrual syndrome (38)	2009	Double-blind randomized, placebo-controlled trial (Severe PMS women)	Three groups, 1: two tablets each contained 5 mg dydrogesterone, 2: two tablets each contained 500mg Ca/200 mg vitamin D, 3: two placebo tablets from day 15 to 24 of two menstrual cycles	Symptom severity was decreased in all 3 groups Decrease in severity is more related to emotional symptoms

Calcium-regulating hormones across the menstrual cycle: evidence of a secondary hyperparathyroidism in women with PMS (39)	1995	One patient with PMS was treated with Ca/vitamin D3 for three months	Symptoms of PMS were ameliorated in treated patient
Vitamin D and calcium in menstrual migraine (40)	1994	Two patients with PMS and menstrually-related migraines were treated with Ca/vitamin D for 2 months	Menstrual migraine attacks and PMS symptoms were decreased

women without PMS symptoms experience more gradual declining pattern of progesterone during luteal phase compared to PMS cases. Women with PMS experience a sharp drop in progesterone level in late luteal phase after an almost stable progesterone levels during most of the secretory phase (10).

Besides the pattern of progesterone fluctuations, progesterone metabolites have important role in pain establishment. Progesterone is converted to neurosteroids like pregnanolone and allopregnanolone during its metabolism and these metabolites play critical roles in PMS manifestations (6). Negative mood symptoms of PMS patients are recorded in allopregnanolone concentrations which are similar to their natural serum concentrations in luteal phases. In higher or lower concentrations, the mood symptoms are alleviated (11). This pattern could be symbolized as a reverted U shape pattern.

As allopregnanolone and pregnanolone are positive allosteric modulators in GABA system (12-14) and GABA-receptor is the prominent inhibitory system in CNS (15), we could expect sedative effects for these compounds. Unlike our expectations, it was shown that these neurosteroids could modify the sensitivity of GABA(A) receptor to the ligand and induce pain and irritability instead of expected calming and anxiolytic effects in PMS patients (6, 16). In line with this phenomenon, it was shown that pain sensitivity is increased in luteal phase of menstruation compared to follicular phase (17).

The pain in PMS also could be related to decreased levels of endorphins in these cases (18, 19). There is evidence of upraised cold pain and pressure pain sensitivity in young females with menstrual pains (20). Iacovides et al stated greater pain sensitivity in women with dysmenorrhea along their menstrual cycles (21). Also, increased expression of pro-inflammatory cytokines and decreased levels of transforming growth factor family were reported in women with primary dysmenorrhea (22).

The other cause of pain in PMS is related to prostaglandin production. The urinary excretion of prostaglandin E2 and F2α are decreased in PMS women compared to controls (23). Thus increased levels of these prostaglandins may contribute for pain related findings in PMS women.

Vitamin D3 effects on PMS

Vitamin D3 is a secosteroid hormone with multi-organ targets. There are two main sources for vitamin D3 in human; photosynthesis in skin and food intake. The main circulatory form of vitamin D3 is 25 hydroxy vitamin D3 which resulted from 25 hydroxylation of vitamin D3 in liver (3).

Vitamin D3 has known hormonal, metabolic and immune-modulatory functions in different organ systems including musculoskeletal, cardiovascular (24, 25), immune system (26, 27), reproductive system (28-31) and so on.

Many studies investigated the vitamin D3 in pain syndromes, including PMS (32-34). Next paragraphs discuss vitamin D and PMS literatures.

Search strategy and results

We searched pubmed with these key words “premenstrual syndrome” and “vitamin D”. This search resulted in 26 articles. We found 14 original articles that contained in somehow these key words in their abstracts. We categorized these articles based on study design. In six studies (35-40) the effects of

Table 2: Articles investigated the association between vitamin D levels and PMS.

Article's title	Year	Study design	Results
The relationship between serum vitamin D level and premenstrual syndrome in Iranian women (41)	2016	Case-control study two Iranian groups: 1. PMS group 2. Control group	There was not any significant difference between 25(OH)D levels between two groups.
The association between the risk of premenstrual syndrome and vitamin D, calcium, and magnesium status among university students: a case control study (42)	2015	Case-control study, Two groups (PMS and control) consisted 20-25 years old women	Vitamin D levels are not statistically different between groups (the risk of PMS in association with vitamin D was not measured)
Plasma 25-hydroxyvitamin D and risk of premenstrual syndrome in a prospective cohort study (43)	2014	Prospective cohort study, Two groups were enrolled: 1. PMS cases which are categorized based on time of blood sampling (before or after PMS diagnosis), Group 2. non PMS controls	The overall risk of PMS was not associated with 25(OH) D levels. In cases that develop PMS after blood collection 25(OH)D levels are associated with lower risk of some of PMS symptoms
Premenstrual symptoms in dysmenorrheic college students: prevalence and relation to vitamin D and parathyroid hormone levels (44)	2012	Cross sectional study with recruitment of 18-24 years old women with primary dysmenorrhea,	There is not association between 25(OH)D and premenstrual symptoms in 18-24 years old women with primary dysmenorrhea
Dietary vitamin D intake, 25-hydroxyvitamin D3 levels and premenstrual syndrome in a college-aged population (45)	2010	Cross sectional case control study of women between 18-30 years old	No statistical significant difference in 25(OH)vitamin D levels was seen in PMS cases with minimal, moderate and severe symptoms The levels of 25(OH)D3 were not associated to the risk of PMS
Cyclical changes in calcium metabolism across the menstrual cycle in women with premenstrual dysphoric disorder (46)	2007	cross-sectional prospective study, two groups were included in the study; premenstrual dysphoric	The levels of 25(OH)D3 were not statistically different between two groups

		disorder and control groups	
Calcium-regulating hormones across the menstrual cycle: evidence of a secondary hyperparathyroidism in women with PMS (39)	1995	Case control study, two groups of PMS and control were investigated	The levels of 25OHD was significantly lower in PMS group during all phases of menstruation cycle compared to control group

vitamin D3 supplementation on PMS or its symptoms were studies (Table 1). We found seven articles (39, 41-46) in which the authors study the association between vitamin D levels and PMS (Table 2), from these articles, three (43-45) are related to the risk of PMS. One of these articles is shared between two categories (39). There was an article which was designed based on the vitamin D and calcium intake according to semi-quantitative food frequency questionnaire in PMS and control groups (47). As this study was not based on supplementation of vitamin D, the results were not consisted in table 1.

All of studies related to vitamin D supplementation (35-40) indicated that providing vitamin D3 could ameliorate the severity of the most somatic and affective PMS symptoms. However the optimum dose of vitamin D3 supplementation and also the best duration of treatment for improving the symptoms need to be declared. Also more studies for investigating the effects of vitamin D especially on pain severity seem to be necessary.

Several studies investigated the relationship between 25(OH)D as the main circulatory form of vitamin D and PMS (39, 41-46). The majority of these articles could not show any significant difference between the PMS and control groups (41-46), except for Thys-jacob et al study (39). Also it is important to emphasize that Obeidat et al indicated no association between vitamin D levels and premenstrual symptoms in dysmenorrheic patients instead of PMS ones (44).

Conclusion

Vitamin D could be effective on many PMS symptoms. The exact mechanisms of these actions are not completely discovered. Shipton et al explained proposed effects of vitamin D on chronic pain syndromes (48). Some of these effects could be involved in PMS as well. Vitamin D could inhibit cyclooxygenase 2 and nitic oxide synthase. These effects could result in decreasing prostaglandin and nitric oxide levels, with final pain modulatory effects. Vitamin D as an anti-inflammatory agent could affect PMS through upraising anti-inflammatory cytokines such as transforming growth factor β and decreasing inflammatory ones such as tumor necrosis factor α in CNS. Vitamin D has modulatory effects on neuroexcitation and in this way it could influence pain related symptoms. Vitamin D could upregulate several neurotrophins and also alter neurotransmitter receptors and ion channels in CNS (48, 49). All of above mentioned mechanisms could be involved in pain amelioration in PMS.

This study has 3 main results:

1- The hypothetical mechanisms relating the effect of vitamin D on PMS pain is relatively well described and involves a wide range of anti-inflammatory interactions and neurological mechanisms of chronic pain affected by vitamin D in PMS patients

2- The clinical outcome of PMS patients is not vividly proved to be affected by vitamin D administration in large RCT's; though there are some pro-vitamin D studies, showing clinical effect of vitamin D in PMS

3- Large multicenter clinical studies with valid laboratory bench marking is still needed to make evidence-based decision in order to give supplemental vitamin D in PMS patients to relieve pain; till then, the final word regarding clinical effects of vitamin D on PMS pain is to be said.

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

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