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Original Article

Serum vitamin D concentrations in young Turkish women with primary dysmenorrhea: A randomized controlled study

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ABSTRACT

Objective: This study aims to investigate the possible role of vitamin D deficiency in primary dysmenorrhea by assessing serum 25-hydroxyvitamin D_3 levels in a cohort which includes young Turkish women with primary dysmenorrhea and healthy controls.

Materials and methods: A total of 683 women who were aged between 18 and 25 years and who were consecutively admitted to the study center were eligible. After the exclusion of 55 women, 184 women with primary dysmenorrhea were randomly assigned into the dysmenorrhea group and 184 women without dysmenorrhea were randomly allocated into the control group.

Results: The dysmenorrhea group had significantly less consumption of dairy products ($p = 0.001$), lower serum calcium ($p = 0.001$), lower serum vitamin D ($p = 0.001$) and higher serum parathyroid hormone ($p = 0.001$) than those of the control group. Hyperparathyroidism was significantly less frequent whereas vitamin D deficiency was significantly more frequent in the dysmenorrhea group ($p = 0.001$ for each). The dysmenorrhea patients with vitamin D deficiency had significantly higher visual analogue scale (VAS) scores ($p = 0.001$). Depression, irritability, mood swings, fatigue, headache and breast tenderness were significantly more frequent in the vitamin D deficiency group ($p < 0.05$ for all). The VAS scores of the dysmenorrhea patients correlated positively and significantly with serum parathyroid hormone levels ($r = 0.666$, $p = 0.001$) whereas these VAS scores correlated negatively and significantly with serum vitamin D levels ($r = -0.713$, $p = 0.001$).

Discussion: The significant and positive correlation between vitamin D levels and VAS scores and the significant reduction in serum vitamin D levels of the dysmenorrhea patients designate the possible role of vitamin D deficiency in the primary dysmenorrhea.

Introduction

Primary dysmenorrhea is characterized by uterine cramping which causes suprapubic pain that occurs just before or during menstruation in the absence of any pelvic pathologic conditions. Primary dysmenorrhea is observed in at least half of the menstruating women, often resulting in the interruption of school and work schedules and ultimately leading to educational and economical considerations. Although the pathogenesis of primary dysmenorrhea has not been clarified, it has been proposed that an excessive release of prostaglandins triggers uterine contractions and lower abdominal pain [1,2].

Previously published studies have identified younger age, younger age at menarche, nulliparity, higher and longer menstrual flow, smoking and positive family history as the associated risk factors. These studies have also indicated the possible role of certain nutrients and dietary habits in the etiopathogenesis of dysmenorrhea. For instance, dysmenorrhea is related with irregular eating, obesity and history of an attempt to lose weight. Moreover, it has been found that the intake of caffeine and sugar is increased and the consumption of vegetables and fruits is reduced in dysmenorrhea patients (Table 1) [3–17]. Recently, two Jordanian studies have reported about the relationship between low calcium intake or vitamin D insufficiency and dysmenorrhea in adolescents and young women with dysmenorrhea [18,19]. Such a relationship

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Table 1
Previously published studies on the etiopathogenesis of primary dysmenorrhea.

Authors	Year	Country	Population	Risk factors
Hailemeskel S [3]	2016	Ethiopia	440 women	Nulliparity Positive family history Lower monthly income History of depression/anxiety History of attempt to lose weight Drinking > 4 glasses of tea/day Drinking > 1 bottle of coke/day
Tomás-Rodriguez MI [4]	2016	Spain	306 women	Higher menstrual flow
Pejčić A, Janković S [5]	2016	Serbia	288 women	Younger age at menarche Positive family history Longer menstrual flow Smoking
Ju H [6]	2016	Australia	9067 women	Smoking
Habibi N [7]	2015	Iran	311 women	Younger age Positive family history Higher menstrual flow Shorter intermenstrual period Residing at home
Kural M [8]	2015	India	310 adolescents	Longer menstrual flow Higher menstrual flow Positive family history
Kazama M [9]	2015	Japan	1167 adolescents	Less physical activity Less sleep (< 6 h/day)
Shiferaw MT [10]	2014	Ethiopia	470 women	Longer menstrual flow Positive family history Circumcision
Sahin S [11]	2014	Turkey	520 women	Menstrual irregularity Smoking Positive family history
Beal SJ [12]	2014	USA	262 adolescents	History of depression/anxiety
Ju H [13]	2014	Review of 15 studies		Younger age/Nulliparity Smoking/Substance abuse History of attempt to lose weight Positive family history History of depression/anxiety
Jang IA [14]	2013	Vietnam	3017 women	Younger age Nulliparity Younger age at menarche Higher menstrual flow Younger menstrual flow
Grandi G [15]	2012	Italy	408 women	Younger age at menarche Longer menstrual flow Smoking
Gagua T [16]	2012	Georgia	2561 women	Smoking Positive family history Eating more sugar Skipping meals
Tavallaee M [17]	2011	Iran	381 women	Younger age Positive family history History of depression/anxiety Eating less vegetables and fruits

has been attributed to the physiological effects of calcium on muscle contractility and relaxation [20,21]. Since calcium homeostasis is maintained by the conjoint actions of calcitonin, parathyroid hormone and 25-hydroxyvitamin D_3, it can be expected that these three hormones would also participate in the pathophysiology of primary dysmenorrhea [22,23].

The present study aims to investigate the possible role of vitamin D_3 deficiency in primary dysmenorrhea by assessing serum 25-hydroxyvitamin D_3 levels in a cohort which includes young Turkish women with primary dysmenorrhea and healthy controls.

Material and methods

This prospective, randomized, case-controlled study was approved by the Institutional Review Board and Ethical Committee of Afyon Kocatepe University where it was undertaken from January 2015 to January 2016. Written informed consent was obtained from all participants included in the study.

Study design and patients

A total of 423 women who were aged between 18 and 25 years and who were consecutively admitted to the department of gynecology at the study center were eligible for the study. Twenty-two women who had pelvic pathologies, twelve women who had systemic diseases, ten women who had acute infections, six women who regularly used calcium or vitamin D supplements and five women who refused to participate were excluded. A total of 184 women who had regular menstrual cycles (occurring in 21–35 days, with menstruation lasting 3–7 days) and who experienced at least 4 consecutive painful periods in the past 6 months with the pain starting one day before or on the day of onset of bleeding were randomly assigned into the dysmenorrhea group. Another total of 184 women without dysmenorrhea were randomly allocated into the control group. Randomization was performed by sequentially numbered, sealed, opaque envelopes (Refer Fig. 1).

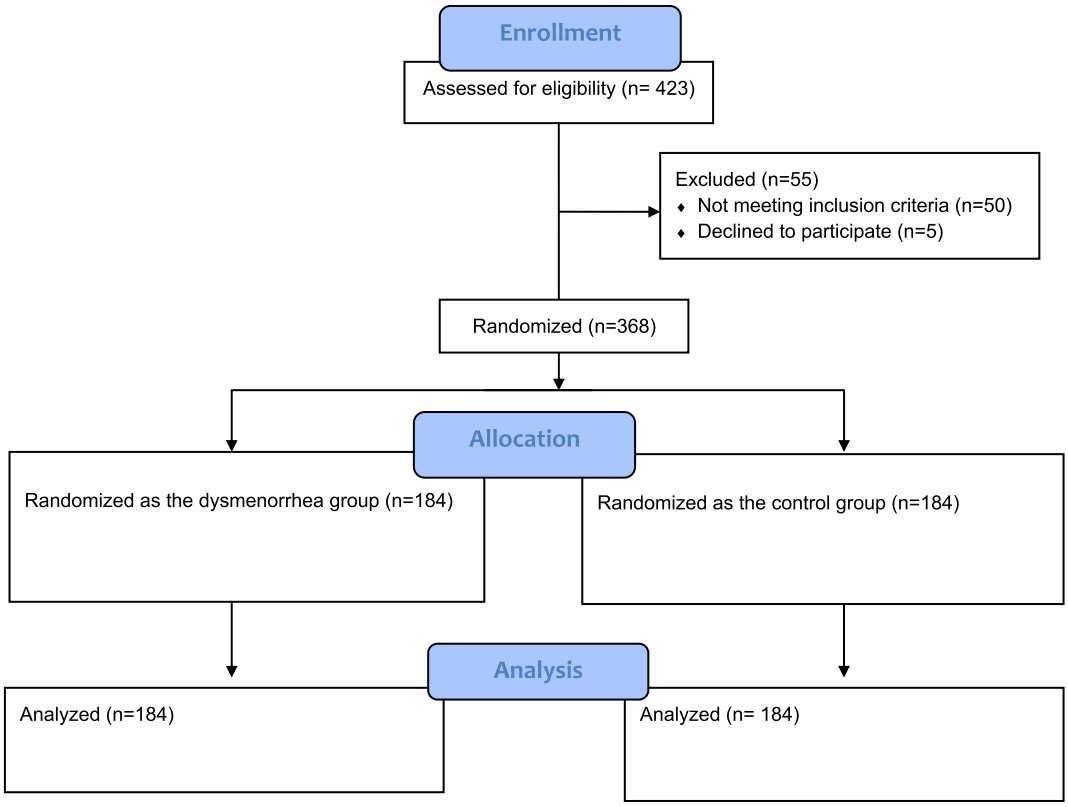

Fig. 1. Flow consort chart of the study.

The participants were instructed to complete a guided self-assessment questionnaire including their demographic features and clinical characteristics about menstruation. Body mass index was calculated as follows: Body mass index (BMI) = Body weight (kg)/Body height^2 (m^2).

The participants also answered questions regarding their consumption of dairy products. The intake of dairy products was determined on daily basis as less than 1, 1 to 2 and more than 2 servings per day. A dairy serving was defined as: 1 cup of milk or yogurt, 2 tablespoons of butter, or 2 tablespoons (or ¼ cup) of cheese.

Moreover, the participants were requested to answer questions about their recurrent experience of 12 physical and psychological symptoms emerging during the premenstrual period. Psychological symptoms of depression, irritability, mood swings, social withdrawal, change in appetite and cravings for sweet or salty foods are recorded, along with physical symptoms such as general fatigue, headaches, nausea, abdominal bloating, and breast tenderness. The severity of dysmenorrhea pain was assessed by using visual analogue scale (VAS) scoring system which is based on numerical rating between 1 and 10.

Laboratory studies

Venous blood samples of 10 ml were collected into heparinized tubes. Serum concentrations of 25-hydroxyvitamin D_3 and parathyroid hormone were measured by a chemiluminescent assay (Elecsys 2010 analyzer, Roche Diagnostics, Mannheim, Germany). The intra-assay and inter-assay coefficients of variation (CVs) for vitamin D were 1.3% and 1.8% respectively while the intra-assay and inter-assay CVs for parathormone were 1.7% and 1.5% respectively. Serum 25-hydroxyvitamin D_3 levels <12 ng/ml indicated vitamin D deficiency and serum parathyroid hormone concentrations >54 pg/ml referred to hyperparathyroidism.

Statistical analysis

Collected data were analyzed by Statistical Package for Social Sciences version 18.0 (SPSS-IBM Inc., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (range: minimum–maximum) whereas categorical variables were denoted as numbers or percentages. Student t-test, chi-square test and Mann Whitney U-test were used for the comparisons. Spearman correlation test was used to detect the correlations among the variables. Two-tailed p values less than 0.05 were accepted to be statistically significant. A *post hoc* analysis was carried out to make a retrospective power analysis and it was determined that a cohort size of 368 women (184 healthy controls and 184 patients with primary dysmenorrhea) had 84.6% power to detect a difference at the 0.05 significance level.

Results

Table 2 compares the demographic, clinical and biochemical characteristics of the dysmenorrhea and control groups. When compared with the healthy controls, the dysmenorrhea patients had significantly more menstrual bleeding ($p = 0.004$), less consumption of dairy products ($p = 0.001$), lower calcium ($p = 0.001$), lower serum 25-hydroxyvitamin D_3 ($p = 0.001$), higher serum parathyroid hormone ($p = 0.001$) and higher VAS scores ($p = 0.001$). Positive family history, vitamin D deficiency and hyperparathyroidism were significantly more frequent in the dysmenorrhea group ($p = 0.001$ for each). Table 3 demonstrates that depression, irritability, mood swings, fatigue, headache, breast

Table 2
Demographic, clinical and biochemical characteristics of the participants.

	Dysmenorrhea patients (n = 184)	Healthy controls (n = 184)	p
Age (years)	20.8 ± 1.9	20.8 ± 2.0	0.957
Weight (kg)	53.8 ± 5.0	53.9 ± 5.4	0.904
Height (m)	1.55 ± 0.05	1.55 ± 0.10	0.793
Body mass index (kg/m^2)	22.46 ± 2.75	22.06 ± 2.43	0.140
Education			0.587 (χ^2 = 1067)
Primary	50 (27.2%)	59 (32.1%)	
Secondary	34 (18.5%)	31 (16.8%)	
High	100 (54.3%)	94 (51.1%)	
Employment			0.119 (χ^2 = 4262)
Unemployed	173 (94.0%)	164 (89.1%)	
Employed	11 (6.0%)	20 (10.9%)	
Menarche (years)	12.2 ± 1.3	12.1 ± 1.2	0.366
Menstrual cycle length (days)	27.3 ± 2.1	27.1 ± 2.3	0.705
Menstrual cycle duration (days)	5.2 ± 0.9	5.0 ± 1.0	0.442
Menstrual bleeding (pads/day)	6.2 ± 1.1	5.9 ± 1.2	0.004*
Positive family history	115 (62.5%)	53 (28.8%)	0.001* (χ^2 = 42,101)
Consumption of dairy products			0.001* (χ^2 = 27,129)
<1 serving/day	139 (75.5%)	91 (49.5%)	
1-2 servings/day	34 (18.5%)	75 (40.8%)	
>2 servings/day	11 (6.0%)	18 (9.8%)	
Serum calcium (mg/dl)	8.3 ± 0.7	8.8 ± 0.9	0.001*
Serum magnesium (mg/dl)	2.1 ± 0.4	2.2 ± 0.5	0.910
Alkaline phosphatase (IU/l)	80.4 ± 24.8	78.8 ± 23.7	0.492
25-hydroxyvitamin D (ng/ml)	7.1 ± 3.8	14.9 ± 2.5	0.001*
25-hydroxyvitamin D deficiency	155 (84.2%)	22 (12.0%)	0.001*
Parathyroid hormone (pg/ml)	66.4 ± 19.5	49.1 ± 13.0	0.001*
Hyperparathyroidism	80 (43.5%)	22 (12.0%)	0.001*(χ^2 = 45,627)
Visual analog scale score	7.3 ± 1.4	2.2 ± 0.9	0.001*

*p < 0.05 was accepted to be statistically significant.

Table 3
Clinical symptoms of the participants.

	Dysmenorrhea patients (n = 184)	Healthy controls (n = 184)	p
Depression	93 (50.5%)	35 (19.0%)	0.001* (χ^2 = 40,298)
Irritability	90 (48.9%)	30 (16.3%)	0.001* (χ^2 = 44,516)
Mood swings	86 (46.7%)	53 (28.8%)	0.001* (χ^2 = 12,590)
General fatigue	86 (46.7%)	44 (23.9%)	0.001* (χ^2 = 20,981)
Headache	82 (44.6%)	57 (31.0%)	0.007* (χ^2 = 7226)
Nausea	44 (23.9%)	52 (28.3%)	0.342 (χ^2 = 0,902)
Social withdrawal	35 (19.0%)	50 (27.2%)	0.064 (χ^2 = 3442)
Abdominal bloating	30 (16.3%)	37 (20.1%)	0.344 (χ^2 = 0,894)
Breast tenderness	26 (14.1%)	11 (6.0%)	0.009* (χ^2 = 6761)
Change in appetite	23 (12.5%)	11 (6.0%)	0.031* (χ^2 = 4666)
Food craving	22 (12.0%)	12 (6.5%)	0.072 (χ^2 = 3241)
Anxiety	14 (7.6%)	11 (6.0%)	0.534 (χ^2 = 0,386)

*p < 0.05 was accepted to be statistically significant.

tenderness and appetite change were significantly more frequent in the dysmenorrhea group (p = 0.001, p = 0.001, p = 0.001, p = 0.001, p = 0.007, p = 0.009 and p = 0.031 respectively).

Table 4 shows that dysmenorrhea patients with 25-hydroxyvitamin D_3 deficiency had significantly shorter height, longer menstrual cycle, longer menstrual bleeding, less menstrual bleeding, less consumption of dairy products and higher VAS scores (respectively p = 0.014, p = 0.002, p = 0.001, p = 0.001, p = 0.001 and p = 0.001). The rates of low education and unemployment were also significantly more frequent in this group (p = 0.001 for both).

Depression, irritability, mood swings, fatigue, headache and breast tenderness were significantly more frequent in the 25-hydroxyvitamin D_3 deficiency group (p < 0.05 for all). However, nausea, social withdrawal, change in appetite and food craving were significantly less frequent in the 25-hydroxyvitamin D_3 deficiency group (p = 0.001 for each) (Table 5).

The VAS scores of dysmenorrhea patients correlated positively and significantly with their BMI (r = 0.242, p = 0.001), menstrual cycle length (r = 0.305, p = 0.001), menstrual bleeding duration (r = 0.271, p = 0.001) and parathyroid hormone levels (r = 0.666, p = 0.001). The VAS scores of dysmenorrhea patients correlated negatively and significantly with their menarche age (r = −0.246, p = 0.001) and serum 25-hydroxyvitamin D_3 levels (r = −0.713, p = 0.001).

Discussion

Vitamin D is a biologically inert molecule which is activated by hydroxylation, first to 25-hydroxyvitamin D_3 by 25α-hydroxylase in the liver and then to 1,25-dihydroxyvitamin D_3 by 1α-hydroxylase in the kidney. This activation process induces the intestinal absorption of calcium and phosphate. When serum vitamin D level decreases, intestinal calcium absorption would be reduced significantly. Then, calcium in the extracellular fluid would decrease and parathyroid hormone release would increase. In turn, parathyroid hormone would enhance the renal reabsorption of calcium and intestinal absorption of calcium and phosphate [23–26].

Risk factors that are associated with dysmenorrhea include younger age, younger age at menarche, nulliparity, higher and longer menstrual flow, smoking and positive family history. The findings of the present study also designate higher menstrual flow and positive family history as the underlying risk factors for dysmenorrhea [3–17]. The possible relationship between dietary habits and dysmenorrhea as well as the widespread location of vitamin D receptors throughout the human body and and the expression of 1α-hydroxylase in decidual cells imply that vitamin D may participate in the pathogenesis of dysmenorrhea [27,28].

This study indicates the overall prevalence of vitamin D deficiency (<12 ng/ml) as 44.5% in a cohort of 398 young Turkish women. This number is compatible with those previously published in literature. The prevalence of vitamin D deficiency was found to be 50.4% in a cohort of 258 healthy Turkish women [29]. Later, Ergur et al. detected moderate vitamin D deficiency in 54.3%

Table 4
Demographic, clinical and biochemical characteristics of dysmenorrhea patients.

	25-hydroxyvitamin D_3 deficiency (n = 155)	25-hydroxyvitamin D_3 normal (n = 29)	p
Age (years)	20.8 ± 1.8	21.0 ± 2.3	0.543
Weight (kg)	53.6 ± 5.2	55.2 ± 4.2	0.112
Height (m)	1.55 ± 0.05	1.57 ± 0.05	0.014*
Body mass index (kg/m^2)	22.48 ± 2.90	22.36 ± 1.68	0.747
Education			0.001* (χ^2 = 24,846)
Primary	50 (32.3%)	0 (0.0%)	
Secondary	33 (21.2%)	1 (3.4%)	
High	72 (46.5%)	28 (96.6%)	
Employment			0.001* (χ^2 = 123,933)
Unemployed	144 (92.9%)	(0.0%)	
Employed	11 (7.1%)	29 (100.0%)	
Menarche (years)	12.2 ± 1.3	12.6 ± 0.9	0.070
Menstrual cycle length (days)	27.5 ± 2.1	26.2 ± 1.6	0.002*
Menstrual cycle duration (days)	5.2 ± 0.9	4.7 ± 0.7	0.001*
Menstrual bleeding (pads/day)	5.7 ± 1.2	6.7 ± 1.2	0.001*
Family history of dysmenorrhea	98 (63.2%)	17 (58.6%)	0.638 (χ^2 = 0,221)
Consumption of dairy products			0.001* (χ^2 = 98,757)
<1 serving/day	136 (87.7%)	3 (10.3%)	0.001*
1-2 servings/day	19 (12.3%)	15 (51.7%)	
>2 servings/day	0 (0.0%)	11 (37.9%)	0.001*
Serum calcium (mg/dl)	8.3 ± 0.7	8.4 ± 0.8	0.455
Serum magnesium (mg/dl)	2.0 ± 0.3	2.2 ± 0.4	0.070
Alkaline phosphatase (IU/l)	81.4 ± 25.1	76.2 ± 23.5	0.271
Parathyroid hormone (pg/ml)	70.5 ± 9.0	47.2 ± 4.4	0.001*
Hyperparathyroidism	74 (47.7%)	6 (20.7%)	0.007* (χ2 = 7275)
Visual analogue scale score	7.6 ± 1.2	5.3 ± 0.5	0.001*

*p < 0.05 was accepted to be statistically significant.

Table 5
Clinical Symptoms of Dysmenorrhea Patients with respect to Vitamin D Status.

	25-hydroxyvitamin D_3 deficiency (n = 155)	25-hydroxyvitamin D_3 normal (n = 29)	p
Depression	93 (60.0%)	0 (0.0%)	0.001* (χ^2 = 35,182)
Irritability	90 (58.1%)	0 (0.0%)	0.001* (χ^2 = 33,416)
Mood swings	86 (55.5%)	0 (0.0%)	0.001* (χ^2 = 30,210)
General fatigue	86 (55.5%)	0 (0.0%)	0.001* (χ^2 = 30,210)
Headache	82 (52.9%)	0 (0.0%)	0.001* (χ^2 = 27,676)
Nausea	25 (16.1%)	19 (65.5%)	0.001* (χ^2 = 32,750)
Social withdrawal	23 (14.8%)	12 (41.4%)	0.001* (χ^2 = 11,172)
Abdominal bloating	23 (14.8%)	7 (24.1%)	0.213 (χ^2 = 1548)
Breast tenderness	26 (16.8%)	0 (0.0%)	0.017* (χ^2 = 5665)
Food craving	11 (7.1%)	11 (37.9%)	0.001* (χ^2 = 22,064)
Change in appetite	10 (6.5%)	13 (44.8%)	0.001* (χ^2 = 24,216)
Anxiety	14 (9.0%)	0 (0.0%)	0.092 (χ^2 = 2835)

*p < 0.05 was accepted to be statistically significant.

of women with singleton term pregnancies and 45.2%of non-pregnant fertile women [30]. In a similar study, the prevalence of severe vitamin D deficiency was 45.9% in a cohort of 229 women with singleton first-trimester pregnancies [31].

The prevalence of vitamin D deficiency and hyperparathyroidism is 84.2% and 43.5% respectively in this cohort of 184 Turkish women with dysmenorrhea. In a study by Abdul-Razzak et al., the prevalence of vitamin D deficiency (<10 ng/ml), vitamin D insufficiency and hyperparathyroidism was 9%, 80% and 48% respectively among 56 young Jordanian women with severe dysmenorrhea [19]. However, vitamin D insufficiency and hyperparathyroidism were observed in respectively 56.5% and 27.6% of young Jordanian women with dysmenorrhea [32]. These contradictory results may be due to the differences in the cut-off values and the timing of blood sampling for parathyroid hormone measurements.

This study indicates that 75.5% of the dysmenorrhea patients consumed <1 serving of dairy products per day and only 6% of these patients consumed >2 servings of dairy products per day. In a study, only 36% of the students who consumed 3 or 4 servings of dairy products per day had severe dysmenorrhea whereas 97% of the students who did not ingest any dairy products complained of severe dysmenorrhea [19]. In a smaller cohort, nearly 50% of the young women with dysmenorrhea had <1 serving of dairy products per day [18]. Vitamin D insufficiency or deficiency has been linked to low socioeconomic status in prior studies [33–35]. Similarly, dysmenorrhea patients with vitamin D deficiency have a low education rate of 53.5% and an unemployment rate of 93% in this study.

The present study points out depression (50.5%), irritability (48.9%), mood swings (46.7%), fatigue (46.7%) and headache (44.6%) as the most frequent premenstrual symptoms. In a Jordanian study, the most commonly encountered premenstrual symptoms were fatigue (72.9%), mood swings (72.3%), anxiety (68.9%), abdominal bloating (68.9%) and depression (58.8%) [32]. Calcium has been addressed as a micronutrient which is directly associated with the severity of premenstrual symptoms. As vitamin D and parathyroid hormone regulate calcium homeostasis, it can be hypothesized that they may also have a role in promoting premenstrual symptoms [36,37]. Accordingly, Bertone-Johnson et al. has related low dietary intake of vitamin D with the emergence of premenstrual symptoms [38]. In addition, it has been demonstrated that high calcium intake or vitamin D supplementation contributes to the alleviation of premenstrual symptoms [39–43]. However, Obeidat et al. were unable to show a significant difference between vitamin D levels of women with and without premenstrual symptoms. They also failed to detect any significant relationship between high dietary calcium intake and premenstrual symptoms except headache and social withdrawal [32].

As for the present study, depression, irritability, mood swings, fatigue, headache and breast tenderness are significantly more frequent while nausea, social withdrawal, change in appetite and food craving are significantly less frequent in the vitamin D deficiency group. Such discrepancies may be attributed to the differences in demographic and clinical characteristics of the reviewed participants and seasonal variations in serum concentrations of vitamin D. The possible correlation between vitamin D deficiency and premenstrual symptoms suggest that vitamin D participates in the etiopathogenesis of these symptoms and vitamin D can be used to treat these symptoms. As known, nearly every tissue and cell type in the body (especially myocardial cells, neurons and adipocytes) has receptors for vitamin D meaning that they all require vitamin D for adequate functioning. Additionally, vitamin D regulates genes that control cell growth and development, immune function, and metabolic control. Any interference with vitamin D metabolism may lead to the psychological, neurological and gastrointestinal symptoms that accompany dysmenorrhea [23–26].

To the best of our knowledge, this is the first randomized controlled study which aims to assess serum vitamin D levels of

young women with primary dysmenorrhea and healthy controls. The significant and positive correlation between vitamin D levels and VAS scores and the significant reduction in serum vitamin D levels of the dysmenorrhea patients designate the possible role of vitamin D deficiency in primary dysmenorrhea. However, the power of this study is limited by two factors. First, this study was undertaken throughout a year and seasonal variations in serum vitamin D concentrations could not be taken into consideration. Second, the patients with known pelvic pathologies and systemic diseases were excluded but clinical entities which could cause pelvic pain and have an accurate diagnosis by interventional methods such as laparoscopy could not be ruled out. Further research is warranted to clarify the role of vitamin D in the pathogenesis of primary dysmenorrhea.

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Conflict of interest statement

The authors declare that they have no conflict of interest.

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