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To cite this article: Ashraf Moini, Tabandeh Ebrahimi, Nooshin Shirzad, Reihaneh Hosseini, Mania Radfar, Fatemeh Bandarian, Shahrzad Jafari-Adli, Mostafa Qorbani & Mahboobeh Hemmatabadi (2016) The effect of vitamin D on primary dysmenorrhea with vitamin D deficiency: a randomized double-blind controlled clinical trial, Gynecological Endocrinology, 32:6, 502-505, DOI: 10.3109/09513590.2015.1136617

To link to this article: http://dx.doi.org/10.3109/09513590.2015.1136617

Published online: 05 May 2016.

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The effect of vitamin D on primary dysmenorrhea with vitamin D deficiency: a randomized double-blind controlled clinical trial

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Abstract

Dysmenorrhea is common among women of reproductive age. This study aimed to investigate the effect of vitamin D (vit D) supplementation in treatment of primary dysmenorrhea with vit D deficiency. A randomized double-blind placebo-controlled clinical trial was conducted on 60 women with primary dysmenorrhea and vit D deficiency referred to our clinic at Arash Women’s Hospital from September 2013 to December 2014. Eligible women were randomly assigned into treatment and control groups (30 in each group). Individuals in the treatment group received 50 000 IU oral vit D and the control group received placebo weekly for eight weeks. After two months of treatment, there was a significant difference in serum vit D concentration between the two groups (p<0.001). Pain severity decreased significantly in treatment group after eight weeks of treatment. There was a significant difference in pain intensity between the two groups after eight weeks of treatment and one month after the end of treatment (p<0.001 for both). A weekly high dose (50 000 IU) oral vit D supplementation for eight weeks in patients with primary dysmenorrhea and vit D deficiency could improve pain intensity.

Introduction

Dysmenorrhea is common among women of reproductive age. Primary dysmenorrhea is a cramping pain in lower abdomen occurring just before or during menstruation without any evident disease or pathology.

The prevalence of dysmenorrhea has been estimated between 45% and 95% [1,2]. The prevalence of dysmenorrhea in Iranian women of reproductive age has been reported from 38.3% to 100% in different regions of the country [3–7]. The difference in the prevalence rate of dysmenorrhea in various studies is due to the different criteria used for definition of dysmenorrhea and probably due to the weather condition of each region. Dysmenorrhea affects quality of women’s life negatively and even limits their activity in severe cases.

Dysmenorrhea begins following the release of prostaglandins from endometrial cells [8]. Therefore, suppression of prostaglandin synthesis or function has been the main therapeutic target in treatment of dysmenorrhea [9]. Till now, different strategies and treatments including non-steroidal anti-inflammatory drugs (NSAIDs), contraceptives, herbal extracts, and supplements have been used for management of menstrual pain [10,11].

Vitamin D (vit D) is a steroid hormone, which is mainly (80–90%) synthesized in the skin by sunlight exposure and its small remaining portion is obtained from the diet and supplements [12].

Prevalence of vit D insufficiency among Iranian girls and boys is 53.6% and 11.3%, respectively [13]. The rate of vit D insufficiency and deficiency in Iran is more than 80% in adults [14,15] while its deficiency is 66.8% in pregnant women [16].

Vit D and vit D receptor (VDR) are involved in calcium (Ca) homeostasis, bone mineralization, and different metabolic pathways in human as well as modulation of reproductive processes in women and men [12]. Endometrium is a target of vit D and 1αOH is expressed in the human uterus [17]. It has been shown that vit D reduces production of prostaglandins [18,19].

The aim of this study was to evaluate the effect of vit D supplement on primary dysmenorrhea in women with vit D deficiency.

Materials and methods

This randomized double-blind placebo-controlled clinical trial was conducted on women with primary dysmenorrhea referred to...
our clinic at Arash Women’s Hospital, Tehran University of Medical Sciences from September 2013 to December 2014.

Ethics Committee at Tehran University of Medical Sciences approved the study protocol with the number of 91-04-39-19158-76257 and informed written consent was obtained from all participants before enrollment. The study was conducted in accordance with the recent version of Helsinki Declaration published in 2013 [20].

Vit D deficiency was defined as follows: mild or insufficient 20–29 ng/mL, moderate or deficient 10–19 ng/mL, severe deficiency <10 ng/mL.

Patients with primary dysmenorrhea aged 18–30 years, having at least four recent consecutive painful menstrual cycles during the past six months, bleeding of 3–7 d, and low serum vit D concentration (<30 ng/ml) were included in the study. Those taking contraceptives within the past two months, using intra-uterine device or drugs containing Ca or vit D within the past six months, smoking and history of renal stones, granulomatous disease, hyperparathyroidism, and any malignancy were excluded. At the same time, before enrollment in the study, secondary causes of dysmenorrhea were ruled out by uterine and ovarian sonography.

Eligible patients were included in the study consecutively and randomly allocated into two groups of treatment and control by block randomization. Individuals in the treatment group (30 patients) received 50 000 IU oral vit D pearl (Zahravi Co., Tehran, Iran) once per week after food and the control group received identical placebo (30 patients) with the same manner for eight weeks.

A questionnaire including demographic information was completed at baseline for all participants. Serum 25-hydroxyvitamin D3, Ca, phosphorus (P), and alkaline phosphatase (AKP) levels as well as pain severity were determined at baseline and at the end of eight weeks of treatment and one month after the end of treatment. Pain severity was measured by visual analog scale (VAS). VAS is a 10-scale pain rank which 0 indicates no pain and 10 indicates very severe pain.

The study was double blind and the physician and patient were blind about the study group. The use of NSAIDs was allowed during the study but the type and dose (number) of it should be recorded in the related form.

Serum vit D concentration was measured by electrochemiluminescence method (Roch Co., Germany). Intra- and inter-assay coefficient of variations (CV) for vit D kit were 4.1–5.7% and 6.6–9.9%, respectively. Serum Ca, P, and AKP concentrations were determined by enzymatic method.

### Statistical analysis

Based on Lasco et al.’s study [18], required sample size with the power of 90% was calculated 25 in each group. Considering loss to follow-up, 20% was added to this number and a sample size of 30 in each group was obtained.

Data analysis was performed using SPSS software version 17.00 for Windows. Results are presented as mean and standard deviation (SD) for numerical data with normal distribution and frequency and percentage for categorical data. Chi-square test was used to compare categorical data between the two groups. As the sample size was less than 30 in each group, nonparametric tests including Mann–Whitney U and Wilcoxon tests were used for comparison of numerical data between and within groups, respectively. To find correlation between two variables Pearson and Spearman correlation tests were applied as appropriate. Also, repeated-measures ANOVA was used to detect the trend of pain score between the groups during the study. p values equal or less than 0.05 were considered significant.

### Results

Sixty women with primary dysmenorrhea aged 18–30 years included in the study. Mean age of women in treatment and placebo groups was 25.91 ± 3.74 and 26.81 ± 2.92 years, respectively without significant difference (p = 0.64). Finally, 23 patients in vit D group and 27 women in control group remained in the study and completed it (Figure 1). In vit D group, 6 women did not use vit D correctly and one patient stopped the use of drug due to increased pain and in control group 2 women became pregnant and one did not refer for follow-up. Among 50 women, 31 (62%) had severe vit D deficiency and remaining 19 patients had moderate vit D deficiency. Demographic characteristics of two study groups have been shown in Table 1. Baseline characteristics of the two study groups were not significantly different (p > 0.05).

Serum concentration of vit D, Ca, P, AKP baseline was not significantly different between the two groups (p > 0.05) (Table 2). After two months of treatment, serum concentration of vit D increased significantly in vit D group but not in the placebo group and there was a significant difference in vit D concentration between the groups (p < 0.001). Other serum biochemical parameters changed as shown in Table 2.

At baseline, in vit D group, pain was mild in 3 patients (13%), moderate in 16 (69.6%), and severe in 4 patients (17.4%) while after treatment 95.7% of patients (22) had mild pain, 4.3% (1) had moderate pain, and none of them had severe pain. In placebo group at the end of two months of treatment, 4 patients (14.8%) had mild pain, 17 (63%) moderate pain, and 6 patients (22.2%) had severe pain. The trend of pain score between the groups during the eight weeks of treatment and one month after the end of treatment has been shown in Figure 2. Although pain severity at baseline was higher in placebo group, as the figure shows, pain intensity reduced significantly in vit D group after eight weeks of treatment and one month after the end of treatment and the trend between the two groups was significant (p < 0.001).

![Figure 1. The study flowchart.](image-url)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Vitamin D group</th>
<th>Placebo group</th>
<th>p Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menarche, year</td>
<td>12.56 ± 1.34</td>
<td>12.88 ± 1.69</td>
<td>0.51</td>
</tr>
<tr>
<td>Gravity, n</td>
<td>0.34 ± 1.07</td>
<td>0.25 ± 0.59</td>
<td>0.90</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.17 ± 3.69</td>
<td>23.74 ± 7.08</td>
<td>0.37</td>
</tr>
</tbody>
</table>

BMI, body mass index.

### Table 1. Demographic characteristics of two study groups.
**Table 2. Different parameters before and after treatment in treatment and placebo group.**

<table>
<thead>
<tr>
<th>Biochemical parameter</th>
<th>Before treatment (mean ± SD)</th>
<th>After treatment (mean ± SD)</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vitamin D group, n = 23</td>
<td>Placebo group, n = 27</td>
<td></td>
</tr>
<tr>
<td>Vit D (ng/mL)</td>
<td>9.69 ± 5.09</td>
<td>11.50 ± 3.73</td>
<td>0.10</td>
</tr>
<tr>
<td>Ca (mg/dL)</td>
<td>9.86 ± 0.30</td>
<td>9.78 ± 0.46</td>
<td>0.44</td>
</tr>
<tr>
<td>P (mg/dL)</td>
<td>3.50 ± 0.27</td>
<td>4.72 ± 6.65</td>
<td>0.81</td>
</tr>
<tr>
<td>AKP (IU/L)</td>
<td>158.88 ± 34.84</td>
<td>186.97 ± 51.68</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>Vitamin D group, n = 23</td>
<td>Placebo group, n = 27</td>
<td></td>
</tr>
<tr>
<td></td>
<td>55.44 ± 6.02</td>
<td>13.57 ± 3.99</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td></td>
<td>9.56 ± 0.38</td>
<td>9.44 ± 0.35</td>
<td>0.38‡</td>
</tr>
<tr>
<td></td>
<td>3.82 ± 0.20</td>
<td>3.56 ± 0.28</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td></td>
<td>146.40 ± 36.38</td>
<td>186.46 ± 52.08</td>
<td>0.003‡</td>
</tr>
</tbody>
</table>

*p < 0.05.
†Mann–Whitney U test.
‡Wilcoxon test.

Figure 2. Trend of pain score between the groups during eight weeks of treatment and one month after the end of treatment.

Number of NSAID used by the patients at baseline was not significantly different between the groups (4.04 ± 2.26 in vit D group and 3.11 ± 2.15 in placebo group, p = 0.14). At the end of two months of treatment, the number of tablets used by the patients decreased significantly in vit D group and there was a significant difference between the two groups (0.91 ± 1.08 in vit D versus 2.11 ± 1.08 in placebo group, p < 0.001). Again, this difference remained significant one month after the end of treatment (p < 0.001).

There was a significant inverse correlation between serum vit D level and pain intensity at the end of eight weeks of treatment and one month after the end of treatment (r = −0.69, p < 0.001 and r = −0.76, p < 0.001, respectively).

**Discussion**

The study results showed that treatment of vit D deficiency in patients with primary dysmenorrhea with vit D deficiency improves dysmenorrheal pain.

Lasco et al., for the first time in 2012, used a single loading oral dose of cholecalciferol for treatment of primary dysmenorrhea. In their study, 20 women received a single oral dose of vit D3 (300 000 IU) just 5 d before the beginning of menstrual cycle and 20 women received placebo. They showed significant effect of vit D in the treatment of primary dysmenorrhea [18]. The results of that study are similar to ours. In Lasco et al.’s study, patients baseline serum 25(OH)D levels were in the lower quartile of the laboratory’s normal range but in our study, women had severe or moderate vit D deficiency. In that study, patients received a single high dose of vit D3 while in our study patients received weekly low dose of vit D (50 000IU) for eight weeks [18].

In our study, after treatment, serum concentration of vit D in treatment group increased from deficiency level to sufficient level but did not reach to high levels. In our study, by increase in vit D concentration pain intensity reduced significantly after treatment. This may indicate that higher levels of vit D may cause more reduction in pain severity. However, this needs to be confirmed in future studies.

As all of patients in our study had vit D deficiency, we could not comment on the effect of vit D supplementation in the treatment of primary dysmenorrhea in those with sufficient vit D concentration. Therefore, yet it remains unknown if dysmenorrhea pain would be improved with vit D supplementation in women with normal baseline serum levels of vit D.

Vit D acts through different mechanisms in improving dysmenorrheal pain in endometrium; in endometrium it reduces expression of cyclooxygenase-2 and consequently reduces prostaglandin production, up-regulates 15-hydroxyprostaglandin dehydrogenase, increases prostaglandin inactivation, regulates the expression of prostaglandin receptor, and consequently reduces pain intensity. Vit D may also act through it anti-inflammatory effects [21,22].

Small sample, short duration of treatment, and follow-up are the main limitations of our study.

Future randomized controlled clinical trials with greater sample size, longer duration of treatment, and different doses of vit D as a maintenance dose and longer follow-up period are required to confirm the efficacy of vit D in treatment of primary dysmenorrhea.

**Conclusion**

Based on the study findings, it seems that vit D supplementation with a weekly dose of 50 000IU for eight weeks could improve pain intensity and decrease the need for using NSAID in patients with primary dysmenorrhea and vit D deficiency.

**Declaration of interest**

The authors have no conflict of interest to report.

**References**

4. Baghiannimoghadam MH, Mohammad Loo A, Fahahzadeh H, Mirzaei Alavijeh M. A survey about the prevalence of dysmenorrhea in female students of Shahid Sadoughi University of Medical


