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Research Article

Designing a Pragmatic Dose-Escalation for Vitamin-D to Reduce Endometriosis-Related Pain after Laparoscopy in Vitamin- D Deficient Women

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ABSTRACT

Objective: the study aimed to discover the subjective cure rate, and the safety of using escalating dose regimens of solubilized cholecalciferol in the medical treatment of endometriosis- related pain after ablative surgeries in vitamin-D deficient women.

Design classification: Prospective study. Setting: Alsaedy Maternity Hospital, Makka, Saudi Arabia. Patients and interventions: In this double-blind clinical trial, we enlisted patients with endometriosis assessed for dysmenorrhea and pelvic discomfort by VAS test at 8 weeks after treatment by laparoscopy. All patients were vitamin-D deficient (<12 ng/ml). They were arbitrarily received vitamin-D (50 000 IU weekly for 6 months) or placebo. Intensity of pain in the 2 groups was reassessed at 6 months after surgery.

Results: There were 25 patients in the vitamin-D group and 25 in the placebo group. Standard features in both groups were analogous. Subsequent to the administration of vitamin-D or placebo, we did not find significant differences in severity of pelvic pain score (p=0.09) and dysmenorrhea score (p=0.366) between the 2 groups. Mean pelvic pain score at 6 months after laparoscopy in the vitamin-D group was 2.96 ± 2 and in placebo group it was 3.3 ± 2 (p=0.55). Mean dysmenorrhea score was 2.44 ± 1.5 in the vitamin-D group and 2.5 ± 1.3 in the placebo group (p=0.88).

Conclusion: After ablative surgery for endometriosis, vitamin-D treatment did not have a noteworthy outcome in decreasing dysmenorrhea and/or pelvic pain.

Keywords: Dysmenorrhea; Endometriosis; Laparoscopy; Vitamin-D.

INTRODUCTION

Vitamin-D status is related to sunlight acquaintance and hence be determined by latitude. Accordingly, vitamin-D deficiency, defined as a serum 25-hydroxy vitamin-D3 (25-OHD3) level < 12 ng/ml, is very common in Northern Europe this is primarily attributed to the lack of enough daylight exposure and low dietary vitamin-D.

Endometriosis is defined as evolution of endometrial glands and stroma outside the uterine cavity. It affects more than 10% of reproductive-age females [1,2]. Endometriosis is an established cause of infertility, pelvic discomfort, dysmenorrhea, and dyspareunia in reproductive-age women. Its diagnosis is by inspection of the pelvis during laparoscopy [1]. In women with pelvic pain and infertility, the incidence of endometriosis is as high as 90%. Pain and subfertility can seriously deteriorate quality of life in affected ladies [3,4].

Endometriosis simulates some autoimmune and neoplastic illnesses, including hereditary manifestations and immunological aberrations in B and T cells, augmented angiogenesis, invasion of endometrial cells to neighboring organs (e.g., bladder and intestine), and demand for repeat surgeries due to recurrence [1,5-7]. Numerous mechanisms for the cause and management of this disease are proposed and the managements are established on these uncertain mechanisms as progestin, GNRH agonists and antagonists [1].

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Also, medications linked to fat metabolism (e.g., Simvastatin) can be administered in some cases [8,9]. It has been revealed that inflammatory mechanism is essential in the occurrence of the disease [10], so management must not be altered from that of other inflammatory illnesses [11]. Vitamin-D levels may be linked to many disorders as polycystic ovarian disease, endometriosis, breast and ovarian cancer, increased arterial stiffness in older patients, and myasthenia gravis [12-18]. It is proven now that vitamin-D plays many essential functions as listed.

- A role in normal cellular growth [19].
- Vitamin-D has immune regulatory effects in chronic infla mmatory responses [20].
- Vitamin-D increases anti-infla mmatory cytokines production and decreasespro inflammatorycytokines [19-24].
- Vitamin-D induces apopto sis and suppression of angiogenesis in and in [25-28].

Though an unforeseen correlation between vitamin-D and endometriosis has been described in numerous studies, but the published randomized clinical trial on endometriosis and vitamin-D treatment in females are still very few. We revealed the relationship between vitamin-D and endometriosis in a double-blind, randomized clinical trial concentrating at the effect of vitamin-D supplementation on alleviation of pain after laparoscopic diagnosis and management.

PATIENTS AND METHODS

This randomized, double-blind clinical trial was accomplished in a single tertiary hospital from Jan 2018 to Dec 2020. A total of 50 patients with established vitamin-D deficiency (serum 25-OHD3 level <12 ng/ml) were included.To find patients with endometriosis, laparoscopy was done for numerous symptoms, as ovarian cyst, infertility, pelvic pain, and dysmenorrhea.

During laparoscopy, endometriosis was diagnosed with trying to excise or ablate all diseased tissue. The day before laparoscopy, a data collection form was completed by a physician, including the reason for laparoscopy, and the severity of pelvic pain and dysmenorrhea were estimated using a visual analogue scale test (VAS test), with a score of 0 being no pain and a score 10 being the worst pain ever experienced. The laparoscopies were done by 2 gynecologic laparoscopic surgeons; both were involved in each operation and they recorded the severity of endometriosis according to the revised American Society for Reproductive Medicine (ASRM) classification [1].

In the patients with endometriosis in the second menses after laparoscopic diagnosis and treatment, the VAS test was repeated. Inclusion and exclusion criteria are mentioned in Table 1.

Inclusion criteria	Exclusion criteria
Women aged 15-40 years with proven endometriosis by Laproscopie	Patients without vitamin-D treatment m the last 6 months prior to surgery
Low serum vitamin-D (< 12 ng/ml)	Patients with known systemic diseases (e.g., hype1tension, diabetes, coronmy, renal, and hepatic diseases)
	Patients with known malignancy.
	Menopausal women
	Patients with hormonal treatment, including oral contraceptive pills, in the last 6 months.

Table 1: Inclusion and exclusion criteria.

After authorization by the Hospital Ethics Committee, eligible patients were assigned by simple randomization to receive either vitamin-D or placebo. In the vitamin-D group (D group), we prescribed oral vitamin-D 50 000 iu/weekly for 6 months and in the placebo group (P group) we prescribed 1 capsule of placebo weekly for 6 months. VAS test was repeated for the 2 groups. Statistical analysis: Retrieved data were recorded on an investigative report. The data were analyzed with SPSS® for Windows®, version 15.0 (SPSS, Inc, USA).

RESULTS

In table 2, the mean age of participants in group I was 27.48±9.5 years and in group II was 26.84 ± 3.25. Causes of laparoscopy in women with endometriosis diagnosed by laparoscopy were dysmenorrhea (n=22 in group I and 22 in group II), ovarian cyst (n=4 in group I and 7 in group II), chronic pelvic pain (n=23 in group I and 21 in group II), and infertility (n=15 in group I and 17 in group II). In some patients, there was more than 1 reason for laparoscopy. Severity of endometriosis were nearly similar in both groups (P>0.05) (Table 2).

	Group I (vitamin-D group)	Group II (placebo) group	P value
Age (mean ± SD)	27.48 ± 9.5 years	26.84 ± 3.25	0.7513
Marriage	19/25	18/25	0.747
BMI (mean ± SD)	24.7 ± 2.1	25.2 ± 2.1	0.4041
Ovarian cysts	4 out of 25	7 out of 25	0.305
Infertility	15/25	17/25	0.555
Severity of endometriosis			
Minimal	12	13	>0.05
Mild	6	4	
Moderate	4	6	
Severe	3	2	

Pelvic pain	23/25	21/25	0.348
Dysmenorrhea	22/25	22/25	1
Serum vitamin-D	10.54 ± 0.88	10.41 ± 0.92	0.608
Pelvic pain score	3.76 ± 2	4.8 ± 2.25	0.0905
Dysmenorrhea score	4 ± 2.25	4.52 ± 1.75	0.3663
Pelvic pain score	3.64 ± 2	4 ± 2.25	0.5527
Dysmenorrhea score	3.24 ± 1.5	3.6 ± 1.7	0.4311
Pelvic pain score	2.96 ± 2	3.3 ± 2	0.5506
Dysmenorrhea score	2.44 ± 1.5	2.5 ± 1.3	0.8805

Table 2: Comparing group I (vitamin-D) group and group II (placebo group) as regarding the baseline characters and pain score before and after laparoscopy

Before laparoscopy, the mean pelvic pain score in the vitamin-D group was 3.76 ± 2 and 4.8 ± 2.25(p=0.0905) in the placebo group. Before laparoscopy, the mean dysmenorrhea pain score in the vitamin-D group was 4 ± 2.25 and in placebo group it was 4.52 ± 1.75 (p=0.3665). a comparison between the 2 groups for severity of pelvic pain and/or dysmenorrhea at different time points (before laparoscopy, in second menses after laparoscopy, and at 6 months after laparoscopy). At the second menses after laparoscopy, there was no significant difference between the 2 groups for pelvic pain (p=0.55) and dysmenorrhea (p=0.43), and at 6 months after laparoscopy there was no significant difference between mean pain scores in the 2 groups.

Mean pelvic pain at 6 months after laparoscopy in the vitamin-D group was 2.96 ± 2 and in placebo group it was 3.3±2 (p=0.55). Mean dysmenorrhea was 2.44±1.5 in the vitamin-D group and 2.5 ± 1.3 in the placebo group (p=0.88). Table 3 and 4 shows a comparison among the means before and after laparoscopy in group I and II respectively by one way analysis of vaiance (ANOVA) with no significant difference in pelvic pain score but the improvement in dysmenorrhea score (Tables 3 and 4).

Group 1	Before laparoscopy	Second menses	After 6 months	P -value
Pelvic pain score	3.76 ± 2	3.64 ± 2	2.96 ± 2	0.318
Dysmenorrhea score	4 ± 2.25	3.24 ± 1.5	2.44 ± 1.5	0.011*

Table 3: Comparing the means before and after laparoscopy in group I by one way analysis of vaiance (ANOVA).

Group 2	Before laparoscopy	Second menses	After 6 months	P -value
Pelvic pain score	4.8 ± 2.25	4 ± 2.25	3.3 ± 2	0.06
Dysmenorrhea score	4.52 ± 1.75	3.6 ± 1.7	2.5 ± 1.3	0.01*

Table 4: Comparing the means before and after laparoscopy in group II by one way analysis of vaiance (ANOVA).

DISCUSSION

In this double-blind, randomized clinical trial, at 6 months after laparoscopic treatment of endometriosis there was no significant difference between effect of vitamin-D 3 (cholecalciferol) and placebo on severity of dysmenorrhea and/or pelvic pain. A study on vitamin-D receptor gene polymorphism in endometriosis compared 132 infertile women with endometriosis with 132 fertile women, reporting no significant difference and suggesting that vitamin-D receptor gene polymorphism does not play an important role in the pathogenesis of endometriosis [29].

In some studies, higher plasma levels of 1, 25-dihydroxy vitamin-D 3 and higher intake of dairy foods was associated with lower risk of endometriosis [30,31]. Conversely, another study compared serum vitamin-D levels of 87 women with endometriosis with 53 women without endometriosis; the mean serum levels of 1, 25-dihydroxy vitamin-D 3 in women with and without endometriosis were 24.9 ± 14.8 ng/ml and 20.4 ± 11.8, respectively (P=0.05) and the study concluded that endometriosis is associated with higher serum levels of vitamin-D [32]. A systematic review of 10 case-control studies and 1 cohort study on women's diet found that women with endometriosis had lower consumption of vegetables and omega-3, and reported a significant association between diet and endometriosis [33].

Vitamin-D binding protein (DBP) is a plasma glycoprotein that modulates immune and inflammatory responses and also controls transport of vitamin-D metabolites and bone development [34]. In a study comparing 13 ectopic endometrial tissues and 6 normal endometrial tissues, vitamin-D binding protein was significantly higher in the ectopic endometrial tissues (P<0.05) [35]. A systematic review of research from 1946 to 2013 on vitamin-D and endometriosis reported that women with endometriosis had higher serum levels of vitamin-D binding protein [36]. Another study compared serum and peritoneal levels of DBP in 26 women with endometriosis and 17 women with other benign gynecological conditions and reported that women with endometriosis had higher serum levels of DBP than in the control group [37]. A study comparing urinary levels of DBP in 57 women with endometriosis with levels in 38 controls found that the urinary level of DBP was significantly higher in patients with endometriosis [38].

A study using a rat model of endometriosis reported that treatment with vitamin-D 3 produced fibrosis and apoptosis in the stroma of tissues with endometriosis [28]. A study on

induced endometriosis in adult Balb female mice reported that administration of 100 μg/kg/day Elocalcitol (a vitamin-D receptor agonist) for 3 weeks reduced total lesion weight [39].

Because a relationship between vitamin-D and endometriosis has been suggested by multiple studies, and since there has been no randomized clinical trial on endometriosis and vitamin-D treatment in women, we decided to explore this relationship. In the present study on endometriosis-related pain, we found no significant difference in results of vitamin-D treatment *vs.* placebo at 24 weeks after surgical diagnosis and treatment [40-43].

Vitamin-D is a fat-soluble vitamin mainly produced in the body from food and supplements and cutaneous sun exposure. Vitamin-D deficiency is defined as serum 1.25-dihydroxy vitamin-D 3 levels under 20 ng/ml. Vitamin-D deficiencies are prevalent worldwide. In the USA, it is reported in 52% of black and Hispanic adolescents in Boston and in 48% of girls in Maine, and it is seen in 40–100% of elderly men and women in the USA and Europe [44]. A study in Germany found that 57% of people 18–79 years old were vitamin- D deficient [45]. The prevalence of vitamin-D deficiency was reported to be 90% in healthy subjects in Delhi, India [46]. In a systematic review of 195 studies in 44 countries found that 37.3% of studies found that the mean serum vitamin-D levels were less than 20 ng/ml [44]. The prevalence in pregnant Turkish women was 81.4% [47]. In a study of high school students in Iran, the serum mean vitamin-D level was 14.7±9.4 ng/ml [48]. In another study in university students in Shiraz, Iran, 51.2% of female students had low serum levels of vitamin-D [49].

Because the incidence of vitamin-D deficiency in Iran is high and we did not check the serum vitamin-D levels in samples before intervention, it is possible that this dose and duration of vitamin-D prescription was beneficial only for treatment of vitamin-D deficiency and not endometriosis.

In 1072 women attending an infertility center, the prevalence of low serum vitamin-D 3 levels was 89%. Vitamin-D 3 levels were reported to be positively associated with height and endometriosis history [40]. An in *vitro* study compared the effect of vitamin-D 3 on 25 human endometriosis stromal cell cultures (ovarian endometrioma) with the effect of vitamin-D 3 on culture of 20 endometrial samples of non-endometriosis women; vitamin-D 3 inhibited proliferation, invasion, and pro-inflammatory cytokine production in endometriosis and reduced production of interleukin 6 and other inflammatory cytokines that stimulate adhesion of endometrial cells to the peritoneal cavity [41].

A study on in *vitro* effects of vitamin-D 3 on human endometriosis stromal cells found that vitamin-D 3 significantly reduced interleukin 1β and tumor necrotizing factor-α inflammatory responses, and also reported fewer endometrial stromal cells and reduced DNA synthesis. The study found significantly lower serum vitamin-D 3 levels in severe endometriosis compared to normal controls and patients with mild endometriosis [42].

A study in Italy investigated the effect of vitamin-D on primary dysmenorrhea. The samples were 40 women aged 18–40 years old with 4 consecutive painful periods in the past 6 months. They measured the serum levels of 25 hydroxy vitamin-D with high-performance liquid chromatography. Then the women were randomized into a group of 20 women who received a single oral dose of 300000 IU vitamin-D (cholecalciferol) at 5 days before their next menstrual cycle and another group of 20 women received placebo. There was a negative correlation between the baseline dysmenorrhea pain score and the level of 25 hydroxy vitamin-D 3 ($r=0.36$, $p=0.2$).

The researchers found a significant reduction of dysmenorrhea pain in the vitamin-D group in comparison with the placebo group in the next 2 menstruations ($p<0.01$). They suggested this significant reduction of dysmenorrhea pain in vitamin-D prescription group was due to decreased levels of pro-inflammatory cytokines and decreased the biological activity of prostaglandins [43]. The samples were not assessed for existing endometriosis. Because low levels of serum vitamin-D are common in healthy Italian pre-menopausal women [43], these results only show that vitamin-D was effective in relieving dysmenorrhea at least for 2 months after treatment in women with or without endometriosis and also in women with or without vitamin-D deficiency [50].

CONCLUSION

There may be a relationship between vitamin-D and pathogenesis of endometriosis, but in our study vitamin-D was not effective in treatment of endometriosis-related pain. Larger clinical trials are needed to determine the possible effects of vitamin-D supplementation in endometriosis treatment.

STUDY LIMITATIONS

The first limitation of this study is the high prevalence of vitamin-D deficiency in our country and worldwide, meaning that a high percentage of our samples may have had vitamin-D deficiency, which may have affected the results of our research. The second limitation is the small sample size of our study.

Further clinical trials are needed on the role of vitamin-D treatment for endometriosis-related pain. Future studies should assess the serum levels of vitamin-D before enrolling study subjects, and those with vitamin-D deficiency should be excluded. Clinical trials with larger sample sizes will be able to produce more reliable results.

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