Vitamin D Supplemental Therapy for Women with Endometriosis may ameliorate Endometriosis-associated Pelvic Pain

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Abstract

Objectives: Evaluation of the effect of 12-wk vitamin D supplemental therapy (VDST) on serum levels of 25-hydroxy vitamin D (25OH-VD) and endometriosis-related pain scores in women with endometriosis

Patients & Methods:41 women with endometriosis were evaluated for presence and severity of dysmenorrhea, dyspareunia and non-menstrual pelvic pain and gave blood samples for estimation of serum 25OH-VD level. All women received VDST as 5000 units/day for 12 weeks and clinical pain scores and serum 25OH-VD were re-evaluated.

Results: After VDST, median value of total pain score was decreased by 25% and the frequency of patients had mild pain was increased by 1.5 folds, while the frequency of patients had severe pain was decreased by 50%. Moreover, the frequency of patients dependent on gabapentin alone or with injectable NSAID was reduced by 75% with concomitant increased frequency of patients dependent on oral NSAID by 2.2 folds. Furthermore, VDST increased serum 25OH-VD levels by 25% with concomitant decreased frequency of women had VD deficiency (VDD) by 1.3 folds. There was negative significant correlation between change of serum 25OH-VD levels and total pain score.

Conclusion: VDD is widespread between women with endometriosis. VDST for 12-wk improved VD sufficiency status and endometriosis-related pain scores.

Keywords: Endometriosis, Vitamin D, Vitamin D Supplemental Therapy, Endometriosis-associated pain

Introduction

Vitamin D (VD) is a secosteroid with a pleiotropic role in multiple physiological processes [1]. It is fat-soluble vitamin acting through VD receptor, which is expressed in most of non-skeletal tissues [2], to affect multiple biologic functions [3]. VD can regulate both innate and adaptive immunity through regulation of cell proliferation, differ-

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entiation and apoptosis [4] and can influence interleukin expression and antimicrobial responses [5].

Serum 25-hydroxy VD (25OH-VD) levels are variable in women and are higher in non-pregnant than in pregnant women and in non-pregnant tends to change during phases of the ovulatory cycles; being higher during luteal than follicular phases [6]. Moreover, VD is synthesized in female reproductive tissues and components required for its synthesis are expressed in the ovary, decidua, endometrium and placenta [7].

Endometriosis is multifactorial disorder, which is dependent on intrinsic and extrinsic factors, but inflammation and immune cell deregulation seems to play a pivotal role in pathogenesis of endometriosis and associated infertility [8]. The immune system abnormalities demonstrated in endometriosis may reflect either chronic inflammatory response or an autoimmune reaction to the presence of ectopic endometrial tissue [9]. Endometriosis could be considered as an autoimmune disease because it shares similarities to several autoimmune diseases with special regard to role of the human leukocyte antigen-C genotype, which is an essential regulator of the activity of natural killer cell that is associated with endometriosis progression [9].

Vitamin D deficiency (VDD) was found to be associated with several autoimmune diseases including autoimmune thyroiditis, rheumatoid arthritis, and systemic lupus erythematosus [10], which are more prevalent in adolescents and adult women [11]. Thus, the active VD metabolites are potentially effective in the treatment of several autoimmune diseases most probably through VD modulatory effect on immune system [12]. VD displays its immune regulatory effect via its intracellular receptors that are present in monocytes, macrophages, T cells, B cells, natural killer cells, and dendritic cells [13] to form a heterodimeric complex, which induces engagement of VD response element and recruitment of activators and enzymes with histone acetylation activity to induce structural changes in chromatin and regulation of targeted gene [14].

Hypothesis

This study supposes that VDD may have a possible relation to the development of endometriosis and so VD supplemental therapy (VDST) may help to minimize the severity of associated manifestations.

Objectives

Evaluation of the effect of 12-wk of vitamin D supplemental therapy (VDST) on serum levels of 25-hydroxy vitamin D (25OH-VD) and on endometriosis-related pain scores in women with endometriosis

Designn

Prospective comparative interventional study

Setting

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Patients & Methods

The present study was started since July 2018 to Jan 2021 to allow evaluation of changes at the end of the 12-w VDST for the last enrolled case. The study protocol was approved by the Local Ethical Committee and women who signed a written fully informed consent to participate in the study were included. All women who attended the Outpatient Clinic of Obstetrics and Gynecology Department, at Benha University hospital with clinical manifestations suggestive of endometriosis or with previously diagnosed endometriosis were eligible for evaluation.

Inclusion criteria

Endometriosis was clinically diagnosed according to the guidelines of the International

Classification of Disease (15) depending on the presence of dysmenorrhea, dyspareunia and non-menstrual pelvic pain (NMPP) in a woman free of other pathologies giving a similar clinical picture.

Exclusion criteria

Presence of other pathologies giving a clinical picture mimics that of endometriosis, presence of other causes of types of pain similar to that caused by endometriosis, refusal to participate the study.

Clinical evaluation

- Demographic data including age, weight and height for calculation of body mass index (BMI) as weight (kg)/ height (m^2) [16] and women were classified according to BMI using the World Health Organization ranges as underweight: BMI<18.5 kg/m^2, normal weight: BMI=18.5-24.9 kg/m^2, overweight: BMI=25-29.9 kg/m2 and obese: BMI=≥30 kg/m^2 [17] .

- History taking concerned with family history of endometriosis, autoimmune diseases, presence of diabetes mellitus, essential hypertension, kidney diseases, previous gynecological surgeries, and previous treatment for endometriosis.

- Number of living offspring, current status of fertility and if infertility was a complaint, data related to its duration, possible causes and previous management was collected.

- Diagnosis and evaluation of endometriosis-related pain

A. Types and severity evaluation

1. Dysmenorrhea was diagnosed on fulfillment of five criteria: hypogastric pain during menstruation, radiating to the lower back, lower limbs, or inguinal region with an intensity of ≥2 on the Wong–Baker scale during the last 3 months, causing inability to perform daily activity and need for analgesia (18). Severity of dysmenorrhea was evaluated and scored using the WaLID score that entails evaluating four variables each of which was scored on 4-point scale (0-3) for a total score ranged between 0 and 12. The variables of WaLID score include working ability evaluating if pain is disabling to perform usual activities (never, almost never, almost always, always), anatomical location and irradiation of pain (No, one site, 2-3 sites, ≥4 sites), pain intensity as evaluated using Wong–Baker pain range (No, hurts a little, little more-to-even more, hurts a lot-lot more) and was scored on 4-point scale (0-3) (19) during the last three months and number of days of pain (0, 1–2, 3–4, ≥5) during menstruation [20].
2. Dyspareunia, is a descriptive term for pelvic or vaginal pain associated with intercourse and was evaluated using Marinoff Dyspareunia Scale, which scored the sexual function in relation to pain on a 4-point scale as no pain with intercourse (score=0), pain with intercourse doesn't prevent the completion (score=1), requiring interruption or discontinuance (score=2) or preventing any intercourse (score=3) [21].
3. Non-menstrual pelvic pain (NMPP) was measured using a 4-point pain-effect scale ranging from 0 (no pain) to 3 (severe pain).
4. Total pelvic pain score: pain intensity of dysmenorrhea, NMPP, and dyspareunia was ranging between 0 and 3 for each item for a total pain score ranging between 0 and 9.

B. Duration of pain was defined as the length of time between onset of pain and enrolment in the study

C. Type of analgesia used was scored on 4-point scale as drug score; non-steroidal anti-inflammatory drugs; oral (score=1), or injectable (score=2), gabapentin or similar drugs (score=3) or both analgesic modalities (score=4).

- Complete gynecological examination for presence of pelvic and/or abdominal tenderness, hematuria or rectal bleeding

Transvaginal Ultrasonography (TVU)

TVU imaging was done (Hitachi EUB-5500) using examining vaginal probe (10-3 MHz), curve probe (5–1 MHz) and linear probe (12–3 MHz) according to the International Deep Endometriosis Analysis (IDEA) Consensus Group (22). The stage of endometriosis was scored according to the revised American Society for Reproductive Medicine (rASRM) score [23].

Evaluation of VD sufficiency status

Random blood samples were obtained under complete aseptic conditions from the antecubital vein in a plane container and left to clot at room temperature for 30 minutes before centrifugation for 20 minutes at 1,000g. Freshly prepared serum was stored at -20oC till estimation of fasting serum 25OH-VD levels using an ELISA kit (Cayman Chemical, Ann Arbor, MI, USA) [24]. The interassay variation for samples containing high, medium or low levels of VD were 4, 6.3, 6, respectively after samples' levels were measured 60 times each using a single set of reagents as documented by the manufacturer. Vitamin D sufficiency status was defined according to 25OH-VD concentration as follows: ≥75 nmol/L sufficient level, 50-75 nmol/L insufficient level and <50 nmol/L deficient level. Vitamin D deficiency was categorized as mild, moderate and severe if 25-OHD concentration was 25-50 nmol/L, 12.5-25 nmol/L and <12.5 nmol/L, respectively [25].

Protocol for VDST

The VDST was provided as rapid release softgel capsule of vitamin D3 once daily, 5000 units/day using Sunvite (Puritan's Pride; Nestlé Health Science S.A, USA) for 12 weeks.

Follow-up

At the 12th week of VDST, all women were evaluated for endometriosis-related pain and gave blood samples for re-estimation of serum 25OH-VD.

Study outcomes

1. The relation between the percentages of changes in serum 25OH-VD and total pelvic pain score at the end of VDST.
2. The prevalence of VDD among the studied population of endometriosis women and the change after VDST.

Statistical analysis

The obtained data were presented as mean, standard deviation (SD), numbers, percentages, median and interquartile ranges (IQR). The percentage of change was calculated as the value determined after VDST minus the value determined before VDST and the difference was divided by the value determined before VDST and multiplied by 100. Parametric data were compared using paired t-test and Mann-Whitney test. Non-parametric data were compared using Chi-square test. Statistical analysis was conducted using the IBM SPSS (Version 23, 2015; IBM, South Wacker Drive, Chicago, USA) for Windows statistical package. P value <0.05 was considered statistically significant.

Results

Throughout the duration of the study, 53 women were eligible for evaluation; 12 were excluded for not fulfilling the inclusion criteria and 41 women were enrolled in the study. Baseline demographic data of enrolled women are shown in table 1.

Table (1): Baseline demographic data

Data			Findings
Age	Categories	<30 years	10 (24.4%)
		30-39 years	17 (41.5%)
		≥40 years	14 (34.1%)
	Mean (SD)		35.2 (7.6)
	Range		23-48
BMI (kg/m^2)	Categories	≤24.9	7 (17.1%)
		25-29.9	23 (56.1%)
		30-34.9	10 (24.4%)
		≥35	1 (2.4%)
	Mean (SD)		35.2 (7.6)
	Range		23-48
Family history of endometriosis	Yes		6 (14.6%)
	No		35 (85.4%)
Smoking history	Yes		4 (9.8%)
	No		37 (90.2%)
No of living offspring	0		7 (17.1%)
	1		14 (34.1%)
	2		15 (36.6%)
	3		5 (12.2%)
Duration of infertility	Categories	<5 years	17 (41.5%)
		≥5 years	24 (58.5%)
	Mean (SD)		5 (1.8)
	Range		2-10

Data are presented as numbers, percentages, mean, SD and ranges; BMI: Body mass index

The presenting clinical manifestations were variable but all patients complained of pain, and 4 patients complained of hematuria (n=1; 2.4%) or rectal bleeding (n=3; 7.3%). Clinical examination detected pelvic tenderness in 17 patients (41.5%) and abdominal tenderness in 8 patients (19.5%). One woman had pelvi-abdominal tenderness and rectal bleeding with occasional hematuria. Rectal bleeding was the main complaint of two women in association with pelvi-abdominal tenderness. WaLID dysmenorrhea scoring illustrated the impact of dysmenorrhea pain on patients' quality of life that was severe for 12 patients (29.3%), moderate in 17 patients (41.5%) and mild in only 4 patients (9.7%), while 8 patients (19.5%) documented no impact of dysmenorrhea on their quality of life (Table 2).

Table (2): WaLID dysmenorrhea score

	Walking ability	Location of pain	Intensity of pain	Days of pain	Total
No	8 (19.5%)	8 (19.5%)	8 (19.5%)	8 (19.5%)	8 (19.5%)
Mild	9 (22%)	24 (58.6%)	18 (43.9%)	12 (29.3%)	4 (9.7%)
Moderate	15 (36.6%)	8 (19.5%)	15 (36.6%)	15 (36.6%)	17 (41.5%)
Severe	9 (22%)	1 (2.4%)	0	6 (14.6%)	12 (29.3%)

Data are presented as numbers, percentages

Mean duration of pain as a complaint was 11.6±4.6 years and only one woman had pain since 20 years and 5 women had pain since less than 5 years. Pain duration was ranging between 5 and 10 years in 12 women (29.3%), between 10 and years in 14 (34.1%) and was in range of 15-20 years in 11 women (26.9%). VDST improved pain scores, regarding dysmenorrhea, dyspareunia and NMPP and total pelvic pain score. Despite the non-significant differences between patients' distribution among pain scores and the non-significant difference in median values of different pain scores; number of patients had mild total pain was increased by 1.5 folds after VDST in comparison to before VDST and number of patients had severe total pelvic pain was decreased by 50% (Table 3).

Table (3): Pain severity scores before and after VDST

Item Grade Time	Dysmenorrhea		Dyspareunia		NMPP		Total	
	Before	After	Before	After	Before	After	Before	After
No	8 (19.5%)	9 (22%)	17 (41.5%)	20 (48.8%)	11 (26.9%)	15 (36.6%)	-	-
Mild	18 (43.9%)	22 (53.6%)	8 (19.5%)	9 (22%)	4 (9.8%)	10 (24.4%)	17 (41.5%)	25 (61%)
Moderate	15 (36.6%)	10 (24.4%)	14 (34.1%)	11 (26.8%)	16 (39%)	11 (26.8%)	14 (34.1%)	11 (26.8%)
Severe	0	0	2 (4.9%)	1 (2.4%)	10 (24.3%)	5 (12.2%)	10 (24.4%)	5 (12.2%)
P value	0.492		0.802		0.123		0.169	
Median score	1 (1-2)	1 (1-1.5)	1 (0-2)	1 (0-2)	2 (0-2.5)	1 (0-2)	3 (1-6.5)	3 (1-5.5)
P value	0.379		0.407		0.072		0.18	

Data are presented as number, percentages, median and interquartile range; p value indicates the significance of difference between before and after VDST; P value <0.05 indicates significant difference; p value >0.05 indicates non-significant difference

The beneficial effect of VDST was reflected on the frequency and score of the use of analgesia, where the frequency of patients required gabapentin alone or with injectable NSAID was reduced by 75% and the number of patients used oral NSAID was increased by 2.2 folds (Table 4).

Table (4): Types and frequency of the used analgesics before and after VDST

Type of analgesia Time	Before VDST	After VDST
Oral NSAID (Score = 1)	5 (12.2%)	11 (26.8%)
Injectable NSAID (Score = 2)	24 (58.6%)	27 (65.9%)
Gabapentin (Score = 3)	4 (9.7%)	1 (2.4%)
Gabapentin + NSAID (Score = 4)	8 (19.5%)	2 (4.9%)
P value	0.049	
Median (IQR)	2 (2-3)	2 (1-2)
P value	0.021	

Data are presented as number, percentages, median and interquartile range; p value indicates the significance of difference between before and after VDST; P value <0.05 indicates significant difference; p value >0.05 indicates non-significant difference

Patients' distribution within the main VD sufficiency statuses showed significant (p=0.011) improvement after VDST with a decreased frequency of women had VDD by 1.3 folds in comparison to the detected distribution before initiation of VDST. Patients' distribution among VDD statuses was significantly (p=0.0315) improved with decreased frequency of patients had severe deficiency by 3 folds (Fig. 1). The mean levels of serum 25OH-VD estimated after 12-wk VDST was significantly (p=0.0122) higher in comparison to mean level estimated before start of VDST with median percentage of increase of 25% (IQR: 11.6-54.35). Total endometriosis-related pain score determined after 12-wk VDST was significantly (p=0.007) lower in comparison to score determined before VDST with median percentage of decrease of 25% (IQR: 0-33.3) (Table 5). Moreover, there was negative significant correlation (Rho=-0.318, p=0.043) between the percentages of change of serum VD and total pain score.

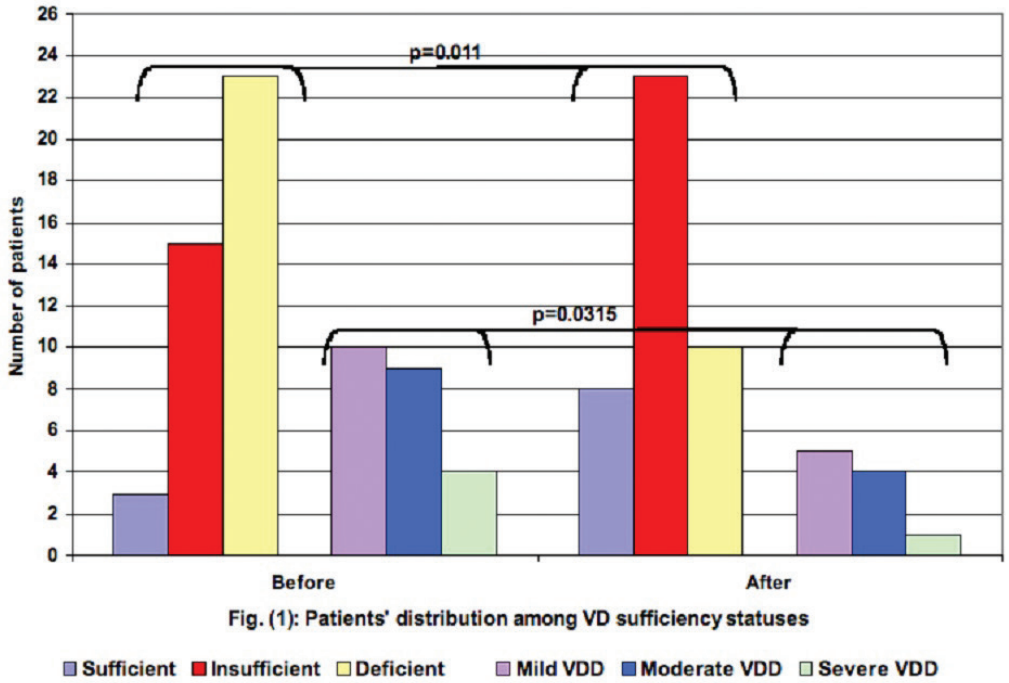

Fig. (1): Patients' distribution among VD sufficiency statuses

Table (5): Serum VD data

P value	After VDST	Before VDST	Data	Time	
0.011	8 (19.5%)	3 (7.3%)	Sufficient		Sufficiency status
	23 (56.1%)	15 (36.6%)	Insufficient		
	10 (24.4%)	23 (56.1%)	Deficiency		
0.0315	5 (12.2%)	10 (24.4%)	Mild		VDD
	4 (9.8%)	9 (22%)	Moderate		
	1 (2.4%)	4 (9.8%)	Severe		
0.0122	55.1 (18.3)	44.1 (20.2)	Mean (SD)		Serum level (nmol/L)
	11-78	9.5-77	Range		
	38.3 (38.1)		Mean (SD)	% of change	
	1.3-138.1		Range		

Data are presented as numbers, percentages, mean, standard deviation (SD), range; VDD: Vitamin D deficiency; P value indicates the significance of difference between before and after VDST; P<0.05 indicates significant difference

Discussion

All enrolled women showed varied degrees of VD deficiency (VDD), apart from three women (7.3%) who had sufficient serum VD level. This finding indicated that VDD is a widespread problem and is coincident with that recently reported in apparently healthy and diseased individuals [26, 27, 28]. VDD was detected in about 93% of the studied endometriosis women; this frequency of VDD indicated a certain relation between VDD and endometriosis. In line with these findings, Ciavattini et al. [29] found a relatively higher rate of women with ovarian endometriosis and VDD and detected a significant linear correlation between 25-OH VD serum levels and diameter of ovarian endometrioma. Qui et al. [30] detected lower VD status in women with endometriosis when compared with controls and a negative relationship between VD levels and severity of endometriosis, and concluded that VDD was a potential risk factor for endometriosis.

Delbandi et al. [31] found 25-OH VD level estimated in serum and peritoneal fluid samples of women with endometriosis were significantly lower than control group and women with serum levels <20 ng/mL had a 2.7 times higher risk of endometriosis than women with serum levels >20 ng/mL and concluded that women with VDD are at higher risk of endometriosis. The obtained results and these findings on literature review were contradictory to that obtained by Somigliano et al. [32] who reported non-significantly higher serum 25-OH VD in women with endometriosis than control and Almassinokiani et al. (33) who reported no effect for VDST. However, Somigliano et al. [32] could not explain their results and attributed the difference to the seasonal effect, which must be the same for all study participants and Almassinokiani et al. [33] used VDST after laparoscopic management of endometriosis and reported non-significant difference in pain which may be attributed to the complexitiy of the disease condition, stimulation of nociceptive cytokines by surgery and this case collection was different than that studied in the current study

Supplemental VD therapy was found to significantly improve serum levels of 25-OH VD with significant improvement of the frequencies of VD sufficiency status. Moreover, there was a positive significant correlation between the percentage of increase of serum 25-OH VD and the percentage of decrease of total pelvic pain scores.

These data illustrate two positive findings; firstly, there is a possible role of VDD for the pathogenesis of endometriosis and may be attributed to improved local and/or systemic inflammatory milieu. In support of the anti-inflammatory effect of VD, Chen et al. [34] detected a negative significant correlation between serum 25-OH VD and IL-6 concentrations in women had tubal factor infertility and considered VDD as a risk factor for this category of infertility. Secondly; the reported improved total pelvic pain score suggested a possible corrective role of VD-ST for endometriosis-associated or -induced manifestations. Similarly, Farland et al. [35] in an interesting observational cohort study, reported that residential ultraviolet (UV) level at birth, at age 15 and 30 were associated with a decreased risk of endometriosis. Clinically, Nodler et al. [36] found adolescent and adult women with endometriosis experienced significant improvement in pain score on VD-ST in comparison to worst pain in the past month. Also, Mehdizadehkashi et al. [37] reported that women with endometriosis who received VD showed significant improvement of pelvic pain scores with significant reduction of levels of total/HDL-cholesterol ratio and high-sensitivity C-reactive protein and significant increase in total antioxidant capacity.

In trial to explain the immunomodulatory effect of VD and the reported effects of VDST, Karagul et al. [38], experimentally, found VD increased P53 mRNA expression in human endometrial cancer cell line (HEC-1A) and caused paraptosis-like HEC-1A cell death. Also, Ghanavatinejad et al. [39] found pretreatment of endometrial cells stimulated by lipopolysaccharide markedly reduced LPS-induced toll-like receptor-4 protein expression with subsequent reduction of activation of nuclear factor-κB intracellular signaling pathway and inflammatory cytokine production and reduction of MyD88 gene expression which acts as an adaptor between extracellular stimuli and intracellular signaling pathways. Clinically, Pazhohan et al. [40] reported that high-dose VD to endometriosis women changed the activity of β-catenin protein, which inhibits Wnt/β-catenin signaling pathway that is responsible for cell proliferation, in blood samples and endometrial biopsies in comparison to control women with endometrium.

The used dose, 5000 U daily for 12 week, provided a cumulative dose of 420,000 U that was coincident with Janice et al. (41) who detected linear increase of serum 25-OH VD with 800 to 4,000 IU/d of vitamin D3 for 16 wk, without a ceiling effect. Also, Khawaja et al. (42) reported no difference in the effect on serum 25-OH VD on using cholecalciferol 50 000 IU/week versus 7000 IU/day for 8 weeks and concluded that timing and frequency of the dosing have no effect on the rise in serum 25(OH)D levels as long as the accumulative dose of cholecalciferol is similar.

Conclusion

VD deficiency is widespread between women with endometriosis. VDST for 12-wk improved VD sufficiency status and is associated with improved pain scores.

Limitation

The study was limited to the duration of VDST and to women with endometriosis-associated dysmenorrhea. Case collection needed to be verifies to exclude those had complicated disease to evaluate the long-term effect of VDST on prevention of disease progression and on fertility in infertile women secondary to endometriosis.

Recommendation

Wider scale study to include women with other pathologies inducing chronic pelvic pain. Evaluation of endometriosis lesions after VDST to assess if there is associated effect.

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