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Efficacy of Vitamin D on Vulvovaginal Atrophy in Menopausal Women: A randomized controlled trial

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ABSTRACT

Objectives: To evaluate the efficacy of oral vitamin D supplementation in improving vulvovaginal atrophy in postmenopausal women over a 12-week period.

Materials and Methods: A double-blind randomized controlled trial involved 48 postmenopausal women with vulvovaginal atrophy. Participants were assigned to receive either 60,000 IU ergocalciferol weekly or placebo. Blinding was applied to both participants and healthcare providers. The primary outcome was vaginal maturation value (VMV) at 12 weeks. Secondary outcomes included VMV at 6 weeks, vaginal atrophy symptoms (VAS), modified vaginal health index (mVHI), vaginal atrophy score (VVA), vitamin D levels, and vaginal pH at 6 and 12 weeks.

Results: Baseline characteristics were not statistically significant between the two groups. In the intention-to-treat analysis, at 12 weeks after treatment, the vitamin D group exhibited significantly higher VMV compared with placebo (47.8 ± 25.24 and 27.4 ± 29.31, $p = 0.027$) and increased superficial cell count ($p = 0.036$). Furthermore, significant improvements in vaginal health index were observed in the vitamin D group at 6 and 12 weeks after treatment (VAS: $p = 0.030$ and $p < 0.001$, mVHI: $p < 0.001$ and $p < 0.001$, VVA: $p < 0.001$ and $p < 0.001$, vaginal pH: $p = 0.001$ and $p < 0.001$, vitamin D level: $p < 0.001$ and $p < 0.001$).

Conclusion: Vitamin D demonstrated superior efficacy over placebo in treating vulvovaginal atrophy in postmenopausal women. Those administered with vitamin D exhibited statistically significant enhancements in vaginal health index, including increased VMV, mVHI, and vitamin D levels, alongside decreased VAS, VVA, and vaginal pH. Therefore, vitamin D may be considered as an alternative treatment option for menopausal women with vulvovaginal atrophy, particularly in those with contraindications to hormone replacement therapy, vitamin D insufficiency, and vitamin D deficiency.

Keywords: postmenopausal women, vulvovaginal atrophy, vitamin D.

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ประสิทธิภาพของวิตามินดีในสตรีวัยหมดระดูที่มีภาวะช่องคลอดแห้ง

ชิโรซา เฮงพระธานี, สิรยา กิติโยดม

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพของวิตามินดีแบบรับประทานในสตรีวัยหมดระดูที่มีภาวะช่องคลอดแห้งตลอดระยะเวลา 12 สัปดาห์*

วัสดุและวิธีการ: *ทำการศึกษาแบบสุ่ม (double-blind randomized controlled trial) ในกลุ่มอาสาสมัครสตรีวัยหมดระดูที่มีภาวะช่องคลอดแห้ง จำนวน 48 คน ณ แผนกผู้ป่วยนอกนรีเวชกรรมและคลินิกผู้สูงอายุ โรงพยาบาลมหาราชนครราชสีมา หลังจากถูกคัดออกตามเกณฑ์การคัดออกผู้เข้าร่วมการวิจัย อาสาสมัครจะถูกแบ่งเป็น 2 กลุ่ม ได้แก่ กลุ่มที่ได้วิตามินดี 60,000 IU ต่อสัปดาห์และกลุ่มที่ได้รับยาหลอก โดยที่อาสาสมัคร แพทย์ พยาบาล ผู้ช่วยพยาบาลและนักเซลล์วิทยาจะไม่ทราบว่าใช้ยาชนิดใด ผลลัพธ์หลักคือค่า vaginal maturation value (VMV) ที่ 12 สัปดาห์หลังรับประทานวิตามินดี ผลลัพธ์อื่นๆที่สนใจ ได้แก่ VMV ที่ 6 สัปดาห์, vaginal atrophy symptoms (the most bothersome symptom) (VAS), modified vaginal health index (mVHI), vaginal atrophy score (VVA), vitamin D level และ vaginal pH ที่ 0, 6 และ 12 สัปดาห์หลังรับประทานยา*

ผลการศึกษา: *ข้อมูลพื้นฐานประชากรทั้งสองกลุ่มไม่แตกต่างกันทางสถิติ นำผลการทดลองที่ได้มาวิเคราะห์ความจำนงในการรักษา (intention to treat analysis) พบว่าที่ 12 สัปดาห์หลังรับประทานยา อาสาสมัครกลุ่มที่ได้วิตามินดีมี VMV มากกว่ากลุ่มที่ได้ยาหลอกอย่างมีนัยสำคัญทางสถิติ (47.8 ± 25.24 และ 27.4 ± 29.3, p = 0.027) และ superficial cell มีจำนวนเพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติ (p = 0.036) นอกจากนี้ยังพบว่าอาสาสมัครกลุ่มที่ได้รับวิตามินดีมี vaginal health index ดีขึ้นที่ 6 และ 12 สัปดาห์ หลังรับประทานยาอย่างมีนัยสำคัญทางสถิติ (VAS: p = 0.030 and p < 0.001, mVHI: p < 0.001 and p < 0.001, VVA: p < 0.001 and p < 0.001, vaginal pH: p = 0.001 and p < 0.001, vitamin D level: p < 0.001 and p < 0.001).*

สรุป: *วิตามินดีมีประสิทธิภาพดีกว่ายาหลอกในการรักษาสตรีวัยหมดระดูที่มีภาวะช่องคลอดแห้ง สตรีวัยหมดระดูที่ได้รับวิตามินดีในการรักษาสภาวะช่องคลอดแห้งมี vaginal health index ดีขึ้นอย่างมีนัยสำคัญทางสถิติ ซึ่งได้แก่ VMV, mVHI และ vitamin D level มากขึ้น ในขณะเดียวกันค่า VAS, VVA และ vaginal pH มีค่าลดลง ดังนั้นวิตามินดีอาจเป็นทางเลือกหนึ่งในการรักษาสตรีวัยหมดระดูที่มีภาวะช่องคลอดแห้งได้ โดยเฉพาะในกลุ่มสตรีที่มีข้อห้ามในการใช้ฮอร์โมนหรือมีภาวะพร่องหรือขาดวิตามินดี*

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Introduction

Vulvovaginal atrophy, a component of genitourinary syndrome, is characterized by the thinning and drying of the vaginal walls, resulting in reduced elasticity and diminished vaginal rugae[1]. Without treatment, the symptoms progressively worsen[2]. This condition is common in postmenopausal women due to declining estrogen and progesterone levels, leading to a decreased proportion of superficial and parabasal cells[3], vaginal wall thinning, lower lactic acid production, increased pH, and bacterial overgrowth, accompanied by reduced lactobacilli levels. These changes result in vaginal inflammation and infection.

The prevalence of vulvovaginal atrophy in the postmenopausal general population is 47%. However, vulvovaginal atrophy is underreported to healthcare professionals, with up to 63% of cases remaining unrecognized[4]. This leads to limited access to and delayed initiation of treatment, resulting in severe symptoms and a low quality of life. The standard treatment for vulvovaginal atrophy is hormonal replacement therapy. Additionally, non-hormonal therapies and alternative treatment options are available for individuals with contraindications to hormone therapy, such as lifestyle modifications, vaginal lubricants, vaginal moisturizers, vaginal laser therapy, and vitamin D supplementation.

Vitamin D also plays a role in influencing the development of vaginal epithelial cells through the vitamin D receptors – Ras homolog gene family – Ezrin pathway (VDR-RhoA-Ezrin pathway)[5]. Moreover, studies indicate that vitamin D deficiency in postmenopausal women reduces vaginal epithelial thickness[5], potentially contributing to vulvovaginal atrophy. Despite Thailand's location within the tropics and its abundant sunlight exposure throughout the year, the prevalence of vitamin D insufficiency is notably high, reaching 45.2%, with vitamin D deficiency reaching 5.7%[6]. The 2011 Endocrine Society Clinical Practice Guideline recommends supplementing 50,000 IU of vitamin D per week for individuals with a deficiency[7]. Previous studies[8-12] in the Middle East and South Asia examined vitamin D supplementation administered orally or vaginally for 8 weeks to 1 year, whereas another study[13] using a lower oral dosage for 12 weeks yielded inconsistent results. This study aimed to evaluate the effects of higher-dose oral vitamin D supplementation for 12 weeks at Maharat Nakhon Ratchasima Hospital, where vitamin D deficiency is prevalent and oral vitamin D is the sole available form. The outcomes of this study may provide benefits for the management of postmenopausal women suffering from vulvovaginal atrophy, potentially alleviating symptoms, promoting the development of vaginal epithelial cells, and ultimately improving their quality of life.

Materials and Methods

A double-blind randomized controlled trial was conducted involving 48 postmenopausal women with symptoms of vulvovaginal atrophy to evaluate the efficacy of 12-week oral vitamin D supplementation in improving their condition. The primary outcome measured was the vaginal maturation value (VMV) at 12 weeks after treatment. Secondary outcomes included VMV at 6 weeks, vaginal atrophy symptoms (the most bothersome symptom) (VAS), the modified vaginal health index (mVHI), vaginal atrophy score (VVA), levels of vitamin D, and vaginal pH at 6- and 12-weeks following treatment. The study protocol was approved by the Human Research Ethics Committee of Maharat Nakhon Ratchasima Hospital (MNRH IRB) with certificate number 083/2023 and registered with the Thai Clinical Trials Registry (TCTR) under certificate number TCTR20231107003.

Postmenopausal women experiencing symptoms of vulvovaginal atrophy were recruited from the outpatient department of gynecology and geriatric clinic at Maharat Nakhon Ratchasima Hospital between July 2023 and February 2024. All participants provided informed consent. The inclusion criteria comprised women with symptoms of vulvovaginal atrophy and postmenopausal status,

defined as the absence of menstruation for more than one year, a history of bilateral oophorectomy, or follicle-stimulating hormone (FSH) levels exceeding 40 IU/L. Exclusion criteria included a history of hormone or vitamin D use within the past 12 weeks, abnormal Pap smear results, active sexually transmitted diseases, abnormal uterine bleeding, severe medical conditions such as liver or renal failure, allergies to vitamin D or calcium, and a history of cancer or radiation therapy.

The sample size was determined based on a pilot study, where participants in the vitamin D group exhibited a mean VMV of 51.55 ± 28.78 at 12 weeks, while those in the placebo group had a mean VMV of 21.00 ± 28.26 at the same time point. The allocation ratio between the vitamin D and placebo groups was 1:1, with an α-error of 0.05 and a β value of 0.01. Additionally, a 25% allowance was made for a potential loss to follow-up, resulting in an adjusted total sample size of 48 participants.

Following the provision of information and informed consent, participants were randomly allocated into two groups: the vitamin D group and the placebo group, with 24 participants assigned to each group. This allocation was achieved through multiblock randomization generated by Microsoft Excel. Subsequently, the randomization sequence was blinded and revealed according to the predetermined order. Blinding procedures were implemented for participants, physicians, nurses, nurse assistants, cytologists, and statisticians involved in the trial throughout the study period. Both the ergocalciferol capsule (20,000 IU per capsule) and the placebo were identical in size, shape, and color. These capsules were repackaged in opaque packets and arranged in sets for 12 weeks, with the order randomized. All participants were instructed to consume either vitamin D or a placebo capsule every Monday, Wednesday, and Friday, accompanied by 1,000 mg of calcium carbonate orally with a meal every morning for 12 weeks. Furthermore, participants received guidance to implement lifestyle modifications and were instructed to refrain from consuming supplementary food, hormones, and herbal medicine throughout the study period.

All participants were provided with questionnaires and completed them independently. The questionnaires included questions about demographic characteristics and vaginal atrophy symptoms (the most bothersome symptoms) (VAS) [14]. Following the completion of the questionnaires, all participants underwent pelvic examinations conducted by second-year residents with one year of practice experience and similar levels of expertise. These examinations were conducted to evaluate vulvovaginal atrophy by assessing mVHI, VVA, vaginal pH, Pap smear, and VMV. Subsequently, blood samples (10 ml) were collected from all participants for vitamin D level analysis.

VMV was determined from cells collected from the upper one-third of the bilateral vaginal wall using the liquid-based technique (EASYPREP®). The collected cells were fixed in a preservation solution, smeared onto slides, and stained for examination by experienced cytologists. One hundred cells were counted and categorized into three types: superficial cells (S), intermediate cells (I), and parabasal cells (P). Subsequently, VMV was calculated using the formula VMV = (0 * P) + (0.5 * I) + (1 * S). VAS was determined through participants answering questionnaires themselves regarding vaginal atrophy symptoms, focusing on the most bothersome symptoms (VAS)[14]. The questionnaires inquired about the severity of symptoms, including vaginal dryness, vaginal itching, vaginal soreness, and dyspareunia. Scores ranged from 0 to 10, where a score of 0 indicated no symptoms, 1-3 indicated mild symptoms, 4-6 indicated moderate symptoms, and 7-10 indicated severe symptoms. mVHI and VVA were determined during the pelvic examination. The mVHI assessed various parameters including vaginal pH, moisture, rugosity, elasticity, length of the vagina, epithelium integrity, and vascularity. The VVA evaluated factors such as vaginal dryness, presence of rugae, vaginal color, existence of petechiae, and mucosal thinning. Vaginal pH was determined using

acid test strips (MQuant®), tested on the posterior upper one-third of the vaginal wall. Vitamin D levels were determined using the electrochemiluminescence immunoassay (ECLIA) technique. Each parameter was examined at 0, 6, and 12 weeks.

At each follow-up at 6 and 12 weeks, all participants were required to bring the remaining ergocalciferol or placebo to the physician for compliance verification and to ensure correct administration. Participants were reminded about proper medication intake, lifestyle modifications, and the importance of avoiding supplementary food, hormones, and herbal medicine throughout the study period. The physician inquired about any symptoms or side effects of the medication and encouraged participants to ask any questions they had or seek additional information.

All statistical analyses were conducted using STATA software. The intention to treat analysis method was employed to analyze the results of this study, which compared data between the vitamin D group and the placebo group. Descriptive statistics were employed to present the data. Independent t-tests were utilized for analyzing normally distributed continuous variables, Fisher's exact test for categorical data, and the Mann-Whitney U test for non-normally distributed continuous variables. Additionally, a repeated measures mixed model was applied for analyzing data with repeated measurements, including VMV, VAS, mVHI, VVA, vaginal pH, and vitamin D level. Statistical significance was considered when the p value was less than 0.05.

Results

Forty-nine postmenopausal women experiencing symptoms of vulvovaginal atrophy were enrolled in the outpatient department of gynecology and the geriatric clinic at Maharat Nakhon Ratchasima Hospital during the study period. One participant was excluded from the study due to an abnormal Pap smear, resulting in a total of forty-eight participants included in the analysis. These participants were then randomly assigned to two groups. By the 12th week, there were seven total losses to follow-up, comprising two from the vitamin D group and five from the placebo group. Thus, the total number of participants available for analysis was forty-one, with twenty-two in the vitamin D group and nineteen in the placebo group. (Fig. 1.)

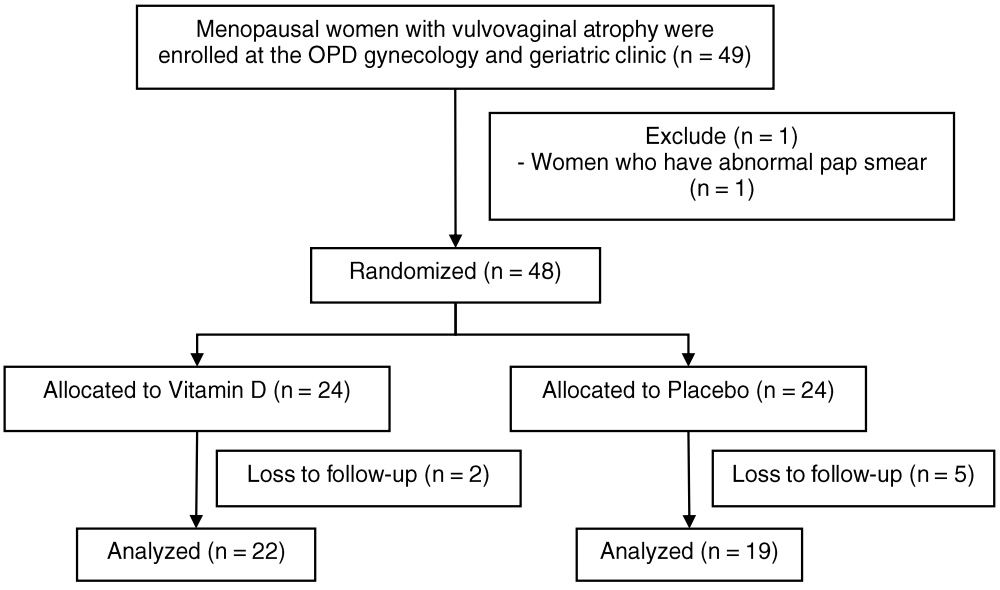


Fig. 1. The study flowchart.

All forty-one participants demonstrated good compliance with taking their assigned capsules. The demographic characteristics of both groups did not reveal significant differences (Table 1). The participants in this study ranged in age from 47 to 84 years. The majority of participants were obese (BMI ≥ 23 kg/m^2), with fifteen in the vitamin D group (68.19%) and ten in the placebo group (52.64%). Only one participant in the vitamin D group reported alcohol consumption, while none reported smoking. Risk factors for vulvovaginal atrophy (such as age at menopause, duration of menopause, active sexual activity, parity, and regular exercise) did not have statistically significant differences between the two groups. Furthermore, the vaginal health index of both groups, including VMV, VAS, mVHI, VVA, and vaginal pH, did not exhibit any significant differences. Most participants exhibited vitamin D insufficiency, and there was no significant difference in baseline vitamin D levels.

Table 1. Demographic characteristics.

Characteristic	Vitamin D (n = 22)	Placebo (n = 19)
Age (years)	65.45 ± 9.56	62.79 ± 7.39
Body Mass Index (kg/m^2)	25.07 ± 3.26	23.40 ± 4.29
Age at menopause (years)	48.27 ± 4.51	48.42 ± 6.39
Menopause duration (years)	17.18 ± 11.66	14.37 ± 9.73
Active sexual activity	9 (40.91)	11 (57.89)
Nulliparous	5 (22.73)	4 (21.05)
Having underlying medical diseases	15 (68.18)	13 (68.42)
Essential hypertension	8 (36.36)	8 (42.11)
Diabetes mellitus	4 (18.18)	2 (10.53)
Dyslipidemia	6 (27.27)	2 (10.53)
Regular exercise	7 (31.82)	6 (31.58)
History of intraabdominal surgery	12 (54.55)	6 (31.58)
Vaginal health measurement and Vitamin D level		
Vaginal maturation value (VMV)	43.64 ± 28.17	27.76 ± 29.44
Vaginal atrophy symptoms (VAS)	10.68 ± 2.30	9.05 ± 3.06
Modified vaginal health index (mVHI)	12.41 ± 1.99	13.21 ± 2.12
Vaginal atrophy score (VVA)	7.59 ± 1.53	6.421 ± 1.71
Vaginal pH	6.43 ± 0.70	6.18 ± 0.79
Vitamin D level (ng/ml)	25.68 ± 8.16	23.66 ± 7.98
Vitamin D deficiency (ng/ml)	16.43 ± 2.23	14.91 ± 5.31
	4 (18.18)	6 (31.58)
Vitamin D insufficiency (ng/ml)	23.79 ± 2.67	25.42 ± 2.85
	13 (59.09)	10 (52.63)
Vitamin D sufficiency (ng/ml)	38.00 ± 6.10	35.3 ± 4.26
	5 (22.73)	3 (15.79)

Data expressed as mean ± standard deviation or n (%)

In the 6th week, the VMV in the vitamin D group increased, though not reaching statistical significance. However, by the 12th week, the VMV in the vitamin D group (47.8 ± 25.24) showed a significant increase compared to the placebo group (p = 0.027). The mean difference (95%CI) was calculated to be 20.45 (2.14, 38.76) (Table 2, Fig. 2).

Table 2. Vaginal maturation value (VMV) between the vitamin D group and the placebo group at 0, 6, and 12 weeks.

Weeks	Vitamin D (n= 22) mean ± SD	Placebo (n= 19) mean ± SD	mean difference (95% confidence interval)	p value
0	43.6 ± 28.17	27.8 ± 29.44	15.87 (-1.58, 33.33)	0.075
6	48.1 ± 28.53	33.6 ± 32.64	14.52 (-3.16, 32.19)	0.107
12	47.8 ± 25.24	27.4 ± 29.31	20.45 (2.14, 38.76)	0.027*

Vaginal maturation value (VMV) = (0*Parabasal cell) + (0.5*Intermediate cell) + (1*Superficial cell)
SD: standard deviation

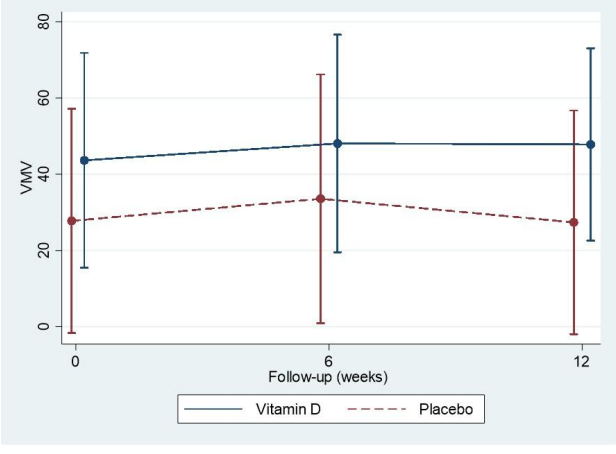


Fig. 2. Mean and standard deviation of vaginal maturation value by time, for the vitamin D and the placebo group.

Comparing the cytological findings of vaginal epithelial cells at the 6th and 12th weeks, it was observed that the vitamin D group exhibited a higher number of superficial cells compared to the placebo group. This increase was statistically significant at the 12th week (p = 0.036). However, no significant differences were observed for intermediate and parabasal cells at either the 6th or 12th week (Table 3).

When comparing other vaginal health indexes, it was found that the vitamin D group exhibited statistically significant improvement over the placebo group at both the 6th and 12th weeks. This improvement included an increase in mVHI and vitamin D levels, as well as decreases in VAS, VVA, and vaginal pH (Table 4, Fig. 3, 4). Moreover, this study did not find any instances of drug allergy or side effects associated with vitamin D, calcium carbonate, and placebo.

Table 3. Comparison of cytological findings between the vitamin D group and the placebo group at baseline, 6 and 12 weeks.

Cytological findings	Vitamin D (n= 22) median (P25, P75)	Placebo (n= 19) median (P25, P75)	p value Mann-Whitney U test
Superficial cell			
Baseline	15 (0,50)	5 (0,30)	0.209
6 weeks	25 (0,40)	5 (0,40)	0.262
12 weeks	30 (0,50)	0 (0,30)	0.036*
Intermediate cell			
Baseline	35 (20,60)	10 (0,40)	0.046
6 weeks	20 (20,60)	30 (0,60)	0.309
12 weeks	30 (20,56)	30 (0,60)	0.224
Parabasal cell			
Baseline	20 (10,80)	80 (10,100)	0.046*
6 weeks	20 (0,60)	35 (10,100)	0.161
12 weeks	25 (10,40)	70 (10,100)	0.076

Data expressed as median (P25, P75)

Table 4. Comparison of vaginal health measurement and vitamin D level between the vitamin D group and the placebo group at baseline, 6, and 12 weeks.

Vaginal health measurement and vitamin D level	Vitamin D (n = 22) mean ± SD	Placebo (n = 19) mean ± SD	mean difference (95% confidence interval)	p value
Vaginal atrophy symptoms (VAS)				
Baseline	10.7 ± 2.30	9.1 ± 3.06	1.63 (0.24, 3.01)	0.021*
6 weeks	2.4 ± 2.02	3.9 ± 2.41	-1.54 (-2.92, -0.15)	0.030*
12 weeks	0.6 ± 0.79	4.5 ± 2.50	-3.89 (-5.28, -2.50)	< 0.001*
Modified vaginal health index (mVHI)				
Baseline	12.4 ±1.99	13.2 ± 2.12	-0.80 (-1.91, 0.30)	0.156
6 weeks	17.5 ± 1.77	14.6 ± 1.92	2.88 (1.77, 3.98)	< 0.001*
12 weeks	18.4 ± 0.96	14.8 ± 1.92	3.57 (2.45, 4.68)	< 0.001*
Vaginal atrophy score (VVA)				
Baseline	7.6 ± 1.53	6.4 ± 1.71	1.17 (-0.15, 2.49)	0.082
6 weeks	3.5 ± 2.84	8.8 ± 3.17	-5.30 (-6.77, -3.82)	< 0.001*
12 weeks	1.3 ± 1.32	6.4 ± 4.17	-5.05 (-6.91, -3.19)	< 0.001*
Vaginal pH				
Baseline	6.4 ± 0.70	6.2 ± 0.79	0.25 (-0.14, 0.64)	0.216
6 weeks	5.8 ± 0.59	6.5 ± 0.65	-0.68 (-1.07, -0.29)	0.001*
12 weeks	5.4 ± 0.57	7.0 ± 0.53	-1.59 (-1.98, -1.20)	< 0.001*
Vitamin D level				
Baseline	25.7 ± 8.16	23.7 ± 7.98	2.02 (-3.78, 7.82)	0.495
6 weeks	43.7 ± 12.61	23.0 ± 6.82	20.70 (14.75, 26.66)	< 0.001*
12 weeks	45.9 ± 12.83	22.3 ± 9.08	23.62 (17.21, 30.03)	< 0.001*

SD: standard deviation

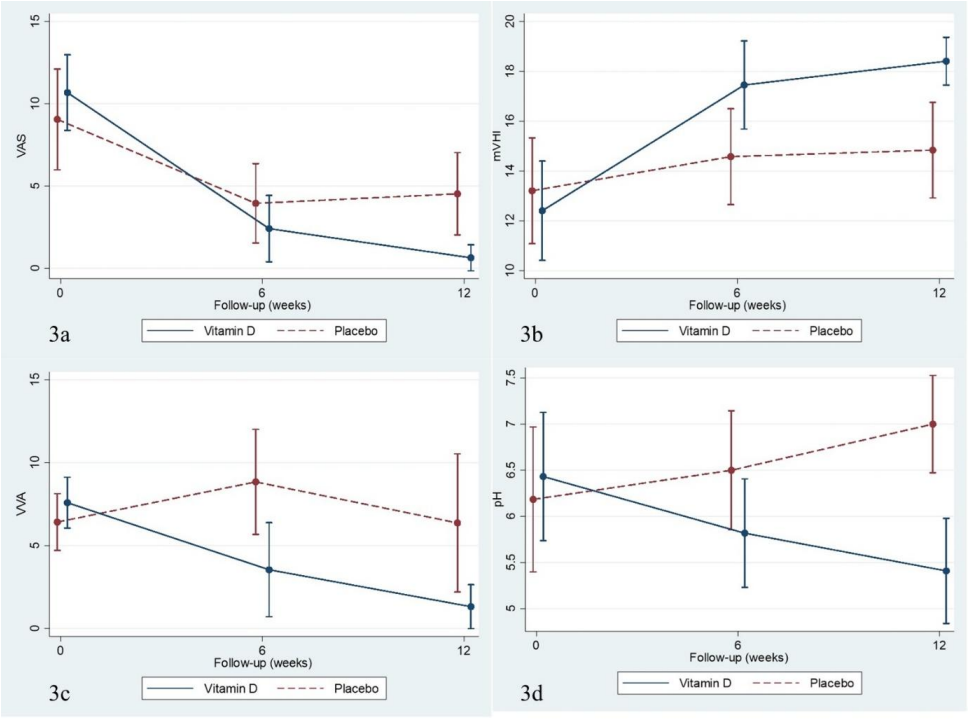


Fig. 3. Mean and standard deviation of (3a) vaginal atrophy symptoms, (3b) modified vaginal health index, (3c) vaginal atrophy score, and (3d) pH by time, for the vitamin D and the placebo group.

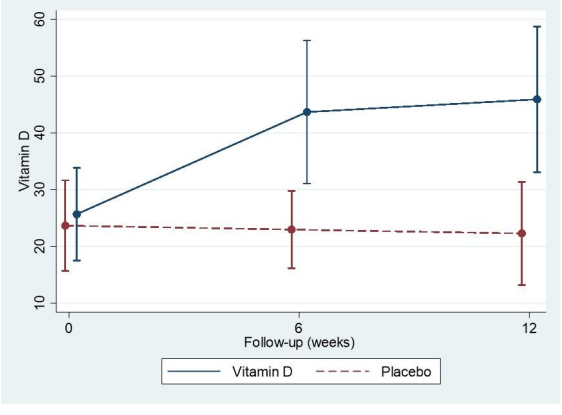


Fig. 4. Mean and standard deviation of vitamin D level by time, for the vitamin D and the placebo group.

Discussion

The administration of a weekly 60,000 IU ergocalciferol supplement for 12 weeks to postmenopausal women experiencing vulvovaginal atrophy resulted in statistically significant improvements in various aspects of the vaginal health index, including increased VMV, mVHI, and vitamin D levels, as well as decreased VAS, VVA, and vaginal pH when compared with a placebo.

At the 6th and 12th weeks, there was a noticeable

increase in the trend of superficial cells, leading to an overall increase in VMV. This could potentially be attributed to the influence of vitamin D on the VDR-RhoA-Ezrin pathway, which affects cell-to-cell junctions, subsequently promoting the proliferation of the vaginal epithelium and increasing superficial cells, and lowering vaginal pH[5].

Additionally, this study observed a significant reduction in VAS scores in the vitamin D group compared to the placebo group at the 6th and 12th weeks. This slightly decrease in the placebo group may be attributed to lifestyle modifications influenced by follow-up advice. Moreover, the VAS is a subjective measure of the most bothersome symptoms, and may also reflect a placebo effect, as noted by Mitchell et al[15]. The findings were consistent with Rad et al[11], which reported significant reductions in vaginal dryness, vaginal pH, and parabasal cell count, alongside increases in superficial cell count after 8 weeks of vitamin D administered via vaginal suppositories. They reported greater changes in parabasal cells, potentially due to the vaginal route facilitating the distribution and absorption of vitamin D into the vaginal epithelium through transcellular transport and receptor-mediated transcytosis[16, 17].

The previous study by Yildirim et al[8], using 20 IU calcitriol daily and calcium supplements in postmenopausal women for one year, reported a statistically significant increase in the percentage of superficial cells and a decrease in basal and parabasal cells in the vitamin D group. However, our study found no significant difference in parabasal cell counts. These may be attributed to our study administering ergocalciferol, an inactive form of vitamin D. While Yildirim et al[8], administered a longer duration of 1,25-dihydroxyvitamin D3 (calcitriol), an active form that can be utilized without undergoing the hydroxylation process in the liver and kidneys.

It's worth noting that, in this study, there was a statistically significant increase in VMV at the 12 weeks. However, Kamronrithisorn et al[13] revealed that the increase was non-statistically significant. This may be due to our study's inclusion of participants with vitamin D insufficiency and deficiency as well as our use of higher ergocalciferol doses, which may lead to a greater increase in VMV.

Furthermore, our study, in accordance with the findings of Bala et al[9] and Kaur et al[10], investigated participants with urogynecological conditions, who exhibited vitamin D deficiency. In both studies, participants were administered 60,000 IU cholecalciferol per week for 10 weeks, followed by maintenance doses every 3 months, resulting in significant increases in mVHI and vitamin D levels.

Moreover, a study by Riazi et al[12] found the appropriate duration for administering vitamin D to observe changes in vaginal health was between 8 to 10 weeks, except for vaginal dryness. This aligned with our findings demonstrated in Fig. 2 to 4. It can be observed that VMV and other vaginal health index improved during the first 0 to 6 weeks after vitamin D supplementation. Despite this, from weeks 6 to 12, the values showed slight improvement and tended to plateau.

Therefore, it may be concluded that vitamin D deficiency or insufficiency could be a contributing factor to worsening vaginal health index and may lead to symptoms of vulvovaginal atrophy. Treatment of vitamin D deficiency or insufficiency may help improve the vaginal health index, including increased VMV, mVHI, and vitamin D levels, and decreased VAS, VVA, and vaginal pH. The effectiveness may depend on the baseline vitamin D level, the form, dosage, duration, and route of vitamin D administration.

This study has several strengths. It was a double-blind study with blinding extended to volunteers, healthcare providers, cytologists, and statisticians. This comprehensive blinding approach helped to reduce bias in the study. Furthermore, the study evaluated the efficacy of vitamin D from multiple perspectives, including self-assessments by participants, physical examinations by physicians, blood tests to measuring vitamin D levels, and cytological evaluations, thereby enhancing its credibility and clarity.

This study also exhibits certain limitations.

Firstly, it was confined to a single center setting and solely investigates the oral administration of vitamin D. The sample size was relatively small, and subgroup analysis of baseline vitamin D levels was not feasible due to the limited number of participants. Future research should involve multicenter studies with larger cohorts to comprehensively explore the efficacy of vitamin D across different routes, dosages, and durations, as well as enable subgroup analysis of baseline vitamin D levels. Moreover, there is a need for clearer assessments of the quality of life and cost-effectiveness of vitamin D supplementation in postmenopausal women with vulvovaginal atrophy, especially for those with contraindications to hormone replacement therapy or those presenting with vitamin D insufficiency and deficiency, to improve patient care and quality of life.

Conclusion

Orally administering ergocalciferol at a dosage of 60,000 IU per week for 12 weeks resulted in a statistically significant improvement in the vaginal health, showing increased VMV, mVHI, and vitamin D levels, along with decreased VAS, VVA, and vaginal pH. These findings suggested that vitamin D could serve as a feasible alternative treatment for postmenopausal women with vulvovaginal atrophy, particularly beneficial for patients with contraindications to hormone replacement therapy or those presenting with vitamin D insufficiency and deficiency.

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Potential conflicts of interest

The author declares no conflicts of interest.

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