Role of Vitamin D in urogenital health of geriatric participants

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ABSTRACT

Introduction: Role of Vitamin D is very well known for the functioning of many body organs. However, its role in the postmenopausal women in relation to various genitourinary disorders has been recognized recently. The main objective of this study was to evaluate role of Vitamin D in vaginal health, prolapse, bladder and bowel function, and bacterial vaginosis (BV).

Materials and Methods: This was a randomized controlled study in which 200 geriatric female patients of 65–78 years of age divided into two groups comprising study and control group with 100 participants in each. Detailed obstetrical, gynecological, and clinical history was elicited. Detailed examination regarding the prolapse, urinary and bowel functions, and bacterial infections was done followed by follow-up of 3 and 6 months each. Chi-square and independent *t*-test used for data analysis.

Results: Mean modified vaginal health index (MVHI) among patients with pelvic floor diseases was statistically significant with P = 0.0472. There was a visible increasing trend in Vitamin D deficiency with increase in time since menopause (P = 0.1193). Patients with pelvic floor disease had mean Vitamin D statistically significant with P = 0.0462. With increase in Vitamin D levels, MVHI was found to be better. The association of mean Vitamin D levels among patients with urinary incontinence as compared to controls was significant with P = 0.0460. Association of mean Vitamin D levels in patients with fecal incontinence and BV as compared to controls was not statistically significant with P = 0.6304 and 0.79, respectively. Low Vitamin D levels were associated with high mean parathyroid hormone (PTH) levels statistically significant with P = 0.034. MVHI was found to increase significantly with Vitamin D supplementation at 3 and 6 months' follow-up. There was increase in Vitamin D and calcium levels and fall in serum PTH levels at 3 and 6 months.

Conclusions: Vitamin D levels were associated with a decreased risk of pelvic floor disorders, improved MVHI in women in geriatric age group.

Key Words: Body mass index, incontinence, modified vaginal health index, parity, pelvic floor disorder, Vitamin D

INTRODUCTION

In India, the average life expectancy for women has increased (more than double) from 23.96 years in 1901 to 62 years in 1999. By 2020, it is projected to reach

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70 years.^[1] Women' health concerning issues emphasize on healthy living including dietary modifications, lifestyle changes, exercise, use of supplemental nutrients as vitamins, minerals, and antioxidants over and above specific medications for disease comorbidities. This has lead to emergence of new concept of Vitamin D deficiency due to sedentary lifestyle remaining indoor, lack of sunshine, and dietary intake leads to deficiency of Vitamin D.

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The sources of Vitamin D are adequate sunshine exposure, normal dietary intake, and pharmaceutical supplementation. The main source of Vitamin D is its skin synthesis under the influence of solar ultraviolet B radiation which accounts for 80%–90% of Vitamin D in humans. In comparison to skin synthesis, the dietary supply of Vitamin D is minor and amounts only to 10%–20% of total Vitamin D; however, it can become a significant source of Vitamin D if enriched with supplementation.

The consequences of Vitamin D deficiency start in the middle age and come to forefront in old age. Thus, elderly are prone to develop Vitamin D deficiency because of various risk factors: decreased dietary intake, diminished sunlight exposure, using sunscreen products, reduced skin thickness, impaired intestinal absorption, and impaired hydroxylation in the liver and kidneys. Furthermore, an increasing epidemic of obesity, which results in sequestration of Vitamin D in adipose tissue, also leads to an increased risk of Vitamin D deficiency.^[2,3]

Although association of Vitamin D deficiency with osteoporosis,^[4,5] viral infections,^[6,7] tuberculosis,^[8-10] HIV,^[11,12] cardiovascular diseases,^[13,14] diabetes,^[15-17] multiple sclerosis,^[18,19] and mortality^[20-22] has been established by many authors, not much research has been done on the association of Vitamin D deficiency with gynecological (urogenital) disorders.

Vitamin D is known to be involved in the regulation of growth and differentiation of body cells, especially squamous epithelium, present in the vagina.^[23] Therefore, this vitamin could be effective in proliferation and repair of epithelial vaginal tissue.^[24] Vitamin D deficiency is associated with bacterial vaginosis (BV), and this link may contribute to the strong racial disparity in the prevalence of BV.^[25,26]

Anatomical and physiological changes in the vagina are associated with postmenopausal decline in circulating estrogen levels and aging. The high concentration of estrogen receptors in the vagina, vestibule, and trigone of bladder modulates cellular proliferation and maturation.^[27,28] Low levels of circulating estrogen after menopause cause biological and physiological changes in urogenital tissues.

Vitamin D receptors are present in human muscle tissue, so a direct effect of Vitamin D on muscle physiology is biologically feasible.^[29] Hence, Vitamin D deficiency has been clinically associated with impaired muscle strength, and loss of muscle mass contributes to the development of poor muscle strength, and this can lead to various pelvic floor disorders (PFDs) such as urinary/fecal incontinence and pelvic organ prolapse (POP).

MATERIALS AND METHODS

This study comprised a total of 200 participants divided into two groups of 100 cases each. Test group (Group A) comprised 100 patients having gynecological diseases associated with Vitamin D deficiency and control group (Group B) comprised 100 participants (normal participants or having generalized nonspecific complaints). Females aged more than 65 years attending the outpatient department/Indoor of Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar, were enrolled in this study. Data thus obtained were statistically analyzed. Participants of more than 65 years of age and those having chronic renal disease, already taking calcium and Vitamin D, were excluded from this study.

An informed written consent of the patient was obtained before inclusion. Clinical history and detailed general physical examination and local pelvic examination were performed as per predetermined parameters. Appropriate laboratory values as per clinical requirement, ultrasound examination for any pelvic pathology, and other relevant investigations related to pelvic floor diseases and tumors were performed.

Classification of urinary incontinence was based on the "incontinence severity index which is a questionnaire composed of two items which assesses the frequency (four levels) and amount (three levels) of urine leakage. The index value (1-12) is reached by multiplying the two items. Women with a score of 3 or higher were considered to be incontinent and those with scores lower than 3 as continent.

Classification of fecal incontinence was based on the Fecal Incontinence Severity Index (FISI) which measured the severity of liquid, solid, mucus, or gas incontinence with severity scale varying from "two or more times per day," "once per day," "two or more times per week," "once a week," to "1–3 times per month." Patient-weighted scores were used to determine severity of symptoms with scores ranging from 0 to 61, where higher scores indicate worse fecal incontinence severity. A FISI score of 0 indicates continence.

Modified vaginal health index (MVHI) was calculated. Seven parameters are included in MVHI. Each parameter is graded from 1 to 3, and total score ranges from 7 to 21. The lower score has greater vaginal atrophy and vice versa [Table 1].

pH was noted by litmus paper kept in the vagina for 1 min and the color compared to standardized colors [Figure 1]. Moisture/consistency of the fluid was measured by putting the vaginal fluid on a clean glass slide for grading [Figure 2]. Kaur, et al.: Vitamin D in urogenital health of geriatric participants

Parameters	1	2	3			
рН	>6.5	5-6.5	<5			
Moisture/consistency	No moisture	Minimal moisture/superficial layer of scanty thin white mucus	Normal moisture/with flocculent fluid			
Rugosity	None	Minimum	Good			
Elasticity	Poor	Fair	Excellent			
Length of the vagina (cm)	<4	4-6	>6			
Epithelial integrity	Petechiae present	Petechiae after scraping	Normal, not friable			
Vascularity	Minimal	Fair	Good			





Figure 1: Comparison method of measuring pH

Rugosity and elasticity was assessed by inspection and palpation of vaginal mucosa by the index finger. Length of the vagina was measured by the index finger and Ayre's spatula from the highest point in the vagina till the vulval outlet. The mean of the two measurements was taken as average length. Epithelial integrity was assessed by the presence of petechiae on the vaginal wall by pressure of index finger. Vascularity was assessed by inspection of the color of the vagina. Prolapse was examined and quantified according to the traditional anatomical site prolapse classification, followed by POP quantification.

Serum 25-hydroxyvitamin D [25(OH)D] 3 levels were measured using enzyme immunoassay (ELISA) kits.

Evaluation of results

Staging of Vitamin D deficiency was done by criteria as follows:

- Deficiency (seriously affected) <12 ng/ml
- Insufficiency <12–30 ng/ml
- Sufficiency (adequately supplied) >30 ng/ml.

The serum Vitamin D levels in geriatric females with gynecological diseases associated with Vitamin D deficiency were compared with control group (normal participants or



Figure 2: Vaginal fluid being transferred to slide for assessment

having generalized nonspecific complaints) to determine the correlation undertaken in this study.

The Vitamin D deficiency was replenished by oral administration of weekly 60,000 IU cholecalciferol granules or tablets in 10 weeks and then every 3 months and followed up till 6 months. The lifestyle dietary modifications were advised. Calcium supplementation 1000–1200 mg daily was advised. The repeat clinical examination, Vitamin D, and other laboratory values were done after 3 and 6 months and improvement reviewed. Selectively, the patients were subjected to other tests related to comorbidities.

RESULTS

Women in the study group ranged from 65 to 78 years of age [Table 2].

Both the groups had comparable number of patients in each age group. Median parity for study group was 5 and for control group was 4 with no significant difference.

Mean body mass index (BMI) for study group was $22.32 \pm 2.67 \text{ kg/m}^2$ and for control group was $21.72 \pm 2.3 \text{ kg/m}^2$. Both groups were BMI matched [Table 3].

Among study group (n = 100), sixty patients fulfilled criteria of pelvic floor disease. Out of them, 30 had POP, 23 had stress urinary incontinence, and 7 had fecal incontinence. Ten patients had culture-proven BV.

Backache was the predominant symptom in study group followed by urinary complaints and dyspareunia. Control group had generalized complaints related to weakness, pain, and occasional urinary symptoms. Mean MVHI among patients with pelvic floor diseases (POP, urinary incontinence, and fecal incontinence) was 12.47 ± 2.61, which was statistically significant with P = 0.0472. It was distinctly clear that participants with PFDs have MVHI more affected than total study (intermediately affected, with MVHI 12.85 ± 2.72) and control group (mean MVHI of 13.4 ± 2.5). Most of the patients with POP were classified as stage III prolapse [Table 4].

No association was found between stage of POP and age. Mean of Vitamin D level in study group was 12.962 ± 7.169 . In controls, the average mean of Vitamin D level was 14.584 ± 7.299 . There was a statistically insignificant overall increase in Vitamin D levels among controls (P = 0.1145). More participants became deficient in Vitamin D with increasing age. The association was found to be statistically insignificant (P = 0.18315). There was a visible increasing trend in Vitamin D deficiency with increase in time since menopause. A statistically insignificant association was found with P = 0.1193. No correlation was seen between Vitamin D and parity (P = 0.350). Nearly 28.6% patients with BMI <18.5 were deficient in Vitamin D as compared to 66.7% of patients with BMI >25. This association was found to be borderline significant with P = 0.093.

Table 2: Age distribution

Age group (years)	Study group (n)	Controls (n)	Р
65-69	47	38	0.316
70-74	33	34	
≥75	20	28	

Table 3: Distribution of participants according to body mass index

ВМІ	Study group	Controls		
Mean (kg/m²)	22.32	21.72	0.0902	

BMI: Body mass index

Table 4: Number of patients in each stage of prolapse

Stage of prolapse	Number of patients	Percentages
Stage 1	3	10
Stage 2	3	10
Stage 3	19	63.33
Stage 4	5	16.66

With increase in BMI, Vitamin D levels were found decreasing in our study. Patients with pelvic floor disease had mean Vitamin D level of 12.09 ng/ml as compared to 14.584 ng/ml in controls. It was found to be statistically significant with P = 0.0462 [Table 5].

All patients with stage I prolapse had Vitamin D levels more than 12 ng/ml as compared to only 67% in stage II, 69% of stage III, and 40% among stage IV prolapse patients. Association was statistically insignificant with P = 0.481. In our study, with increase in Vitamin D levels, MVHI was found to be better. There was positive association with correlation coefficient being 0.239 and P = 0.046, which was statistically significant. In our study, mean Vitamin D level among patients with urinary incontinence was 11.259 \pm 6.315 ng/ml as compared to controls with mean Vitamin D level 14.584 \pm 7.299. Association was found to be statistically significant with P = 0.0460 [Table 6].

In our study, mean Vitamin D level in patients with fecal incontinence was 13.217 \pm 6.28 ng/ml as compared to 14.584 \pm 7.299 ng/ml in controls. The association was not statistically significant with P = 0.6304 [Table 7].

Mean Vitamin D level in patients with BV was 13.685 ± 6.75 ng/ml as compared to 14.584 ± 7.299 ng/ml in controls. The association was not statistically significant with P = 0.709. Mean parathyroid hormone (PTH) level among cases was 38.264 ± 12.233 and controls was 36.584 ± 11.267 . Standard error of mean was 1.223 and 1.1267 in cases and controls, respectively. Low Vitamin D

Table 5: Vitamin D levels in patients with pelvic floordisorders (including pelvic organ prolapse, urinary, and fecalincontinence)

Group	Mean (ng/ml)	SD	SEM	Р	
Study group (n=60)	12.09	6.217	0.8026	0.0462	
Controls (n=100)	14.584	7.299	0.9423		

SD: Standard deviation, SEM: Standard error of mean

Table 6: Correlation of Vitamin D levels with urinary incontinence

Group	Mean (ng/ml)	SD	SEM	Р
Study group (n=23)	11.259	6.315	1.316	0.0460
Controls (n=100)	14.584	7.299	0.729	

SD: Standard deviation, SEM: Standard error of mean

Table 7: Correlation of Vitamin D levels with fecal incontinence

Group	Mean (ng/ml)	SD	SEM	Р
Study group $(n=7)$	13.217	6.28	2.373	0.6304
Controls (n=100)	14.584	7.299	0.729	

SD: Standard deviation, SEM: Standard error of mean

levels were associated with high mean PTH levels. The association was statistically significant with P = 0.034. Seven cases and 13 controls were lost to follow-up at 3 months' interval. At 6 months, further 11 cases and 17 controls were lost to follow-up. Twelve out of sixty cases with pelvic floor disease (including POP, urinary, and fecal incontinence) underwent surgical intervention, and rests of participants were treated conservatively.

Patients with culture proven BV were treated with antibiotics in addition to Vitamin D and calcium supplementation.

MVHI was found to increase significantly with Vitamin D supplementation at 3 and 6 months' follow-up. In the present study, there was increase in Vitamin D and calcium levels and fall in serum PTH levels at 3 and 6 months. Positive clinical response was seen in participants with pelvic organ disease [Tables 8 and 9].

Other participants did not show much improvement.

DISCUSSION

In the study of Badalian and Rosenbaum, the mean menopausal age of women associated with Vitamin D and PFDs was 47.9 (46.4–49.6) years, whereas Parker-Autry *et al.* in a similar study found that women in the PFD group were slightly older than the obstetrics group (64.3 ± 12.6 years vs. 60.2 ± 12.5 years, respectively, P = 0.005).^[30,31] Sharma *et al.* in their study on the role of serum elastin and 25(OH)D levels in women with POP in postmenopausal women (PMW) in study group had average age since menopause was 14.5 \pm 7.60 years in study cases and 9.5 \pm 6.20 years in control group.^[32] Both the groups were comparable without any statistical difference. In contrast to above-cited studies, the present study had more women with time since menopause was >15 years probably because our study had more women in older age group.

In the present study, median parity for cases was 5 and for control group was 4. No significant difference was found in parity for two groups. Similar results were shown by previous studies.^[30,32]

In the present study, mean BMI for study group was $22.32 \pm 2.67 \text{ kg/m}^2$ and for control group was

 21.72 ± 2.3 kg/m². Although BMI was more in study group, both groups were BMI matched and statistically insignificant. Similar trend was seen in a study by Parker-Autry *et al.*^[31] Mean BMI was less in the present study as compared to western data probably due to better care for geriatric patients in west and malnutrition in our country.

In this study, localized symptoms were present in all the patients even in those with prolapse of stage I or II. Previous studies have suggested that the prolapse of stage II or higher is more associated with local symptoms. However, a regular gynecological examination revealed that in patients complaining of local symptoms, only 2% had prolapse that reached the introitus.^[33] Furthermore, the study has indicated that pelvic floor-related symptoms do not predict the anatomical location in women with mild to moderate prolapse, and symptoms such as vaginal heaviness and pressure appear to have a weak relationship with POP which is alike the findings and observations of Badalian *et al.* and Navaneethan *et al.*^[30,34]

Fecal incontinence is a common PFD with an estimated prevalence of 9% in US women aged 20–59 years, increasing to 14.4% in women between 60 and 79 years.^[35] Study by Parker-Autry showed 44 patients out of 374 had fecal incontinence.^[31] Our study differed from some of the previous studies in having slightly less number of patients with fecal incontinence probably because most of women with fecal incontinence in our country do not seek treatment and take self-medications, thus underreporting the true prevalence.

The prevalence of sexual dysfunction in the present study was 30%. The prevalence of sexual symptoms in women with POP (>stage II) ranged between 9% and 57%.^[36] The variation in the prevalence is due to inconsistent definitions. Dyspareunia is multifactorial and is a common in older women; it is due to vaginal dryness as a result of low estrogen.

In this study, mean MVHI was 12.85 ± 2.72 in study group and 13.4 ± 2.5 in controls. Average MVHI among patients with PFD was 12.47 ± 2.61 . Participants with PFDs have MVHI more affected than total study (intermediately affected) and control group which is more or less alike that reported by Sharma *et al.* and Sharma *et al.*^[32,37]

	POP	Urinary incontinence	Fecal incontinence	Bacterial vaginosis	Controls
Beneficial	16	13	3	3	23
Some improvement	8	7	2	4	31
No improvement	5	3	1	2	33
Lost to follow-up	1	0	1	1	13

POP: Pelvic organ prolapse

Table 9: Client response at 6 months						
	Controls					
Beneficial	15	11	2	2	20	
POP: Pelvic organ prolapse						

In the present study, most participants in POP group were classified as stage III prolapse. In the present study, there was no correlation between age and stage of POP, which is different from the study reported by Zong *et al.*^[38] It could be because larger number of patients in our study belonged to stage III as compared to other stages. In the analysis of results of the National Health and Nutrition Examination Survey, increasing age was predicted as a risk factor for PFDs, but they did not examine the patients, hence stage of prolapse was not given.^[30]

In the present study, MVHI was seen to deteriorate significantly with increase in stage of POP. Correlation coefficient was 0.448 and P = 0.013. It shows vaginal tissues wear out with increasing prolapse. This correlation was interesting and explainable as MVHI was affected greatly in 3° prolapse. Study by Sharma *et al.* also showed statistically significant deterioration of MVHI with increasing stage of prolapse.^[32]

CV Harinarayan et al. studied 25(OH)D and bone mineral density in women of reproductive (WR) age group and PMW in South India and reported Vitamin D deficiency in 76% in WR, 70% in PMW, insufficiency in 16.5% in WR, and 23% in PMW.^[39] In the present study, more participants became deficient in Vitamin D with increasing age and increase in time since menopause though the association was found to be statistically insignificant. Similar trends were seen in studies by Badalian et al., Parker-Autry et al., and Sharma et al., all of which showed statistically insignificant increase in the prevalence of Vitamin D deficiency with increasing age.^[30-32] However, in the study by Navaneethan et al., relationships between Vitamin D levels and menopause of more than 5 years remained statistically significant.^[34] In the present study, all the women in study group and 93 participants in control group had Vitamin D \leq 30 ng/m1. The result was in accordance with above-stated studies.

In the present study, no correlation was seen between Vitamin D and parity (P = 0.350). Similar results were shown in studies by Badalian *et al.*,^[30] Sharma *et al.*,^[32] and Navaneethan *et al.*,^[34] in which no statistically significant difference was found between parity and Vitamin D levels.

In the present study, Vitamin D levels showed an inverse relationship with BMI, and this association was found to be borderline significant with P = 0.093 Badalian *et al.* in their

study also revealed an inverse association with 25(OH)D; those with higher BMI had lower 25(OH)D levels.^[30]

In the present study, mean Vitamin D level in overall study group was 12.962 ± 7.169 . In controls, the average mean of Vitamin D level was 14.584 ± 7.299 . There was a statistically insignificant overall increase in Vitamin D levels among controls (P = 0.1145). Patients with pelvic floor disease had mean Vitamin D level of 12.09 ng/ml, which was statistically significant with P = 0.0462. Navaneethan *et al.* in their study found Vitamin D levels to be significantly lower (t = -2.16; df = 98.22; P = 0.034) among cases with PFD (mean 13.15 ng/ml; standard deviation [SD] 1.01) than among controls without PFD (17.98 ng/ml; SD 16.61).^[34] In study by Badalian et al., women with 25(OH)D levels in the normal range (at least 30 ng/mL) had a nonsignificant decreased risk of PFDs compared with women with levels below 30 ng/mL; the adjusted odds ratio (95 confidence interval) was 0.75 (0.54–1.04) (P = 0.084).^[30]

Vitamin D levels were seen to decrease with increasing stage of POP. Association was statistically insignificant with P = 0.481. In the present study, most of the women had stage III prolapse, and women in other stages were quite less; this could be the cause for statistically insignificant results. Similar results were shown in the study by Sharma *et al.*^[32] while most of other studies did not quantified the stage of prolapse.^[33,34]

With increase in Vitamin D levels, MVHI was found to be better in the present study. There was positive association with P = 0.046, which was statistically significant. Similar results were shown in studies by Rad *et al.* and Sharma *et al.*, in which increase in Vitamin D levels showed improvement in MVHI and vaginal pH.^[24,32]

In our study, mean Vitamin D level among patients with urinary incontinence was 11.259 ± 6.315 ng/ml as compared to controls with mean Vitamin D level 14.584 ± 7.299 ng/ml with statistically significant P = 0.0460. The Leicestershire MRC Incontinence Study Group (a longitudinal cohort study) reported that higher Vitamin D intake was significantly associated with reduced risk of overactive bladder onset (P = 0.008).^[40] In our study, no statistically significant association was found between mean Vitamin D levels and fecal incontinence with P = 0.6304. Parker-Autry *et al.* in their study found that women with fecal incontinence had lower Vitamin D levels (mean 29.2 \pm 12.3 cases vs. 35 \pm 14.1 ng/ml controls, respectively, P = 0.04). The odds of Vitamin D deficiency were higher in women with fecal incontinence compared to controls (OR 2.77, 95% CI [1.08-7.09]). Among cases, women with deficient Vitamin D (35%) had higher Modified Manchester Health Questionnaire scores, indicating greater fecal incontinence symptom burden (51.3 \pm 29.3 [Vitamin D deficient] vs. 30 \pm 19.5 [Vitamin D sufficient], P = 0.02).^[31] Badalian *et al.* also showed insignificant decrease in the prevalence of fecal incontinence in participants with higher Vitamin D levels.^[30] This may be secondary to the small number of cases in this subset of PFDs (n = 7). Some women with fecal incontinence may deny symptoms, resulting in underreporting of this disorder.

In the present study, no statistically significant association was found between Vitamin D levels and BV. Bodnar *et al.* in a study found the prevalence of BV to be approximately 57% in women with a serum 25(OH)D concentration of <20 nmol/L and 23% in women with serum 25(OH)D concentration of more than 80 nmol/L. They noted a dose-response association between 25(OH)D level and BV prevalence.^[41] The difference in our study may be due to the fact that we only took cultures of symptomatic patients, and routine screening of asymptomatic women was not done. In the present study, a statistically significant association was found between low Vitamin D and high mean PTH levels with P = 0.034. Our study showed similar results as reported by Need *et al.*^[42]

In our study, Vitamin D and calcium supplementation was given to all participants with Vitamin D insufficiency and deficiency, and all biochemical parameters along with clinical response were noted on subsequent follow-ups after 3 and 6 months. Positive clinical response was seen in participants with POP, urinary incontinence, and BV. Other participants did not show much improvement.

Rad *et al.* in their study found Vitamin D to be effective in improving the maturation index and decreased the pH and dryness of the vaginal atrophy due to menopause.^[24] Taheri *et al.* found that with Vitamin D supplementation, the cure rate of asymptomatic BV was 63.5% in the intervention and 19.2% in the control group (P < 0.001).^[43] In addition, patients with culture-proven BV in our group were also treated with antibiotics which may be a confounding factor in the assessment of outcome.

CONCLUSIONS

The present study showed very high prevalence of Vitamin D insufficiency and deficiency in geriatric women population. Treatment of Vitamin D insufficiency and deficiency in geriatric women could improve pelvic muscle strength, with a possible reduction in the prevalence of PFDs including POP and urinary incontinence and positive impact on vaginal tissues as it improved MVHI. Given the increase in the number of patients with gynecological disorders in geriatric age, further evaluation of the role of Vitamin D as a modifiable causative factor in these diseases is warranted.

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Conflicts of interest

There are no conflicts of interest.

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