



## ORIGINAL ARTICLE

### Relationship Between Vitamin D Deficiency and Menopause Associated Symptoms in Postmenopausal Women

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#### ABSTRACT

**Background:** Menopause is a natural transition marked by decreasing estrogen levels. Vitamin D deficiency is common in postmenopausal women, and it is necessary for calcium absorption and bone health. Although the specific relationship between low vitamin D levels and the severity of menopausal symptoms is uncertain, current study suggests a probable link. The present study aims to explore if there is any association between vitamin D status and the severity of menopause-related symptoms.

**Methods:** This cross-sectional study included 305 postmenopausal women aged 52–64 years at Zagazig University Hospitals. Participants were divided into two groups based on serum 25(OH)D levels: Group I: 98 women with sufficient vitamin D ( $>30\text{ng/ml}$ ). Group II: 207 women with insufficient vitamin D ( $<30\text{ng/ml}$ ). All participants underwent clinical assessment, Menopause Rating Scale (MRS) evaluation and serum vitamin D measurement using the 25-OH vitamin D kit.

**Results:** Vitamin D insufficiency was observed in 52.4% of the studied population. A significant positive correlation was found between vitamin D levels and both age ( $r = 0.238$ ,  $p < 0.001$ ) and menopausal duration ( $r = 0.304$ ,  $p < 0.001$ ), while a negative correlation was observed with BMI ( $r = -0.257$ ,  $p < 0.001$ ) and MRS scores ( $r = -0.178$ ,  $p = 0.003$ ). Vitamin D was identified as an independent negative predictor of MRS scores in multiple regression analysis ( $\beta = -0.267$ ,  $p = 0.003$ ). ROC analysis showed that a vitamin D cutoff of  $26.3\text{ ng/mL}$  predicted severe menopausal symptoms with 88.24% sensitivity and 61.18% specificity (AUC = 0.798).

**Conclusions:** Although some statistically significant correlations were observed between vitamin D levels and certain menopausal symptoms, overall, vitamin D deficiency was not conclusively associated with the severity of menopausal symptoms in this study.

**Keywords:** Menopause; Vitamin D insufficiency; Postmenopausal Women

#### INTRODUCTION

Menopause is defined as the permanent cessation of menstruation, usually occurring between the ages of 45 and 55, with an average age of 51 years. A woman is considered postmenopausal when menstruation has ceased for at least 12 consecutive months and serum follicle-stimulating hormone (FSH) levels exceed  $49\text{ IU/L}$  [1].

Long after their last menstrual cycle, many women still have menopausal symptoms. For instance, hot flashes are common in women 4–10 years following menopause. Mood disorders are also common, though it's unclear how they relate to menopause. These

symptoms may be severe enough to have an adverse effect on one's personal relationships, professional performance, and quality of life. New therapeutic approaches can be developed by identifying the potential mechanisms behind menopause-related symptoms [2].

Vitamin D, a fat-soluble steroid hormone, contributes to calcium and phosphate homeostasis and immune modulation [3]. Its deficiency is common among postmenopausal women and may mirror certain menopausal symptoms such as mood disorders and musculoskeletal pain. Vitamin D is mainly obtained via sun exposure and dietary intake. Its active form, 25-hydroxyvitamin D [ $25(\text{OH})\text{D}$ ], is synthesized in the liver and is

the most reliable marker of vitamin D status [4].

Despite Egypt's sunny climate, vitamin D deficiency remains prevalent among women, possibly due to limited sun exposure and dietary factors [5]. However, the relationship between vitamin D levels and menopausal symptoms remains inconclusive in the current literature. So, the present study aims to explore if there is any association between vitamin D status and the severity of menopause-related symptoms.

### METHODS

This cross-sectional study was conducted in the Obstetrics and Gynecology Department, Zagazig University Hospitals, using a multistage random sampling technique, involving 305 postmenopausal women from September 2023 to September 2024. The local research ethical committee at Zagazig faculty of medicine (institutional research board "IRB") approved the study with (IRB# 11135-20/9-2023). Each participant provided informed written agreement, and confidentiality and personal privacy were respected throughout the study. The study adheres to the World Medical Association's Helsinki Declaration (1975), which serves as an ethical guideline for human subjects research.

#### Sample size:

Based on the total number of postmenopausal women attending the outpatient clinic at Zagazig University Hospitals over a 6-month period (approximately 1,500 patients), and assuming an expected prevalence of vitamin D deficiency of 52%, a 5% margin of error, and a 95% confidence level, the minimum required sample size was calculated to be 305 participants. The calculation was performed using OpenEpi version.

#### Sampling Technique:

A multistage random sampling technique was used. In the first stage, outpatient clinic days were randomly selected across the study period. In the second stage, eligible participants attending on those days were randomly selected using systematic sampling from the patient registry. This method aimed to ensure random representation across clinic days and time points.

The inclusion criteria encompass postmenopausal women who have experienced 12 months in a row with no apparent physiological or medical cause and without clinical intervention, and who report menopausal symptoms. Exclusion criteria include women who are already participating in diet or exercise interventions, those with a history of bariatric surgery, hysterectomy and/or oophorectomy, patients with parathyroid disorders, women taking drugs that are known to influence weight and/or hot flashes, such as gabapentin, selective estrogen receptor modulators (SERMs), selective norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), clonidine, hormone treatment, antipsychotics, steroids, weight loss drugs, or chemotherapy. Additionally excluded are women who suffer from colitis, pancreatic disease, liver disease, malabsorption syndromes, or present gallbladder problems, all of which are linked to vitamin D inadequacy. Women with diseases like hypercalcemia or recent malignancy that may affect vitamin D levels are also ineligible. Finally, participants with insufficient data are excluded.

The trial was open to all postmenopausal women who fulfilled the qualifying requirements. Each participant underwent a comprehensive assessment, including a detailed history focusing on menstrual and reproductive history as well as any existing medical conditions such as diabetes, hypertension, and thyroid disorders. A clinical examination was then performed, and women filled out the Menopause Rating Scale (MRS) in a private room with a researcher on hand to help if necessary. Based on the MRS scores, menopausal symptoms were categorized as mild, moderate, or severe. With domain scores ranging from 0 to 16, the scale comprises 11 symptoms that are divided into three domains: the psychological domain, which includes depression, irritability, anxiety, and physical and mental exhaustion; the urogenital domain, which includes vaginal dryness, bladder problems, and sexual problems; and the somato-vegetative domain, which includes musculoskeletal symptoms (joint and muscle discomfort) and vasomotor

symptoms (hot flashes, heart discomfort, and sleep problems). The possible score ranges from 0 to 44, with each symptom being rated from 0 (none) to 4 (extremely severe). The related **table 1** was then used to classify the overall severity.

#### **Measurement of Vitamin D Using the 25-OH Vitamin D (EIA) Kit:**

A 5-ml blood sample was given by each participant following a 12-hour fast. Centrifugation was used to process the blood samples within an hour of collection, and the serum was separated and kept for analysis at -70°C. Before their clinic consultations, participants were told to avoid alcohol for 48 hours and to engage in rigorous activity for 24 hours. The purpose of the study was to assess the connection between menopausal symptoms and vitamin D levels. 25-hydroxyvitamin D (25-OH Vitamin D) can be quantitatively measured in plasma and serum samples using the Immundiagnostic Enzyme-Immuno-Assay (EIA) kit.

#### **Statistical analysis:**

The collected data were coded, entered, and analyzed using IBM SPSS Statistics version 23.0 for Windows (SPSS Inc., Chicago, IL, USA). The distribution of quantitative variables was assessed using the Shapiro–Wilk test. Normally distributed data were summarized as mean  $\pm$  standard deviation (SD), while non-normally distributed data were presented as median and interquartile range (IQR). Categorical variables were described as frequencies and percentages. For statistical analysis, the chi-square ( $\chi^2$ ) test was used to assess associations between categorical variables, and Fisher’s exact test was applied when more than 20% of expected cell counts were less than 5. For continuous variables, the independent t-test was used for normally distributed data, whereas the Mann–Whitney U test (Wilcoxon rank-sum test) was used for non-normally distributed data. Pearson’s correlation coefficient was used to assess the relationship between normally distributed continuous variables, and Spearman’s rank correlation was applied for ordinal or non-normally distributed data. Multiple linear regression analysis was conducted to identify independent predictors of continuous outcomes such as Menopause

Rating Scale (MRS) scores. Receiver Operating Characteristic (ROC) curve analysis was used to evaluate the diagnostic performance of vitamin D levels in predicting severe menopausal symptoms. A p-value  $\leq 0.05$  was considered statistically significant.

#### **RESULTS**

Two groups of women were selected based on their vitamin D levels: Group I: It included 98 post-menopausal women with sufficient serum 25 (OH) D concentrations ( $>30$  ng/ml). Their ages ranged from 52 to 64 years with mean  $\pm$  SD of  $58 \pm 4.41$ . (32.7%) were married and (67.3%) were widowers. Their height ranged from 135 to 170 cm with median (IQR) of 164 (15). Their weight ranged from 59 to 130 kg with median (IQR) of 89 (28). Their BMI ranged from 32 to 47.7 with a median (IQR) of 32.9 (2.2). Group II: It included 207 post-menopausal women with insufficient serum 25 (OH) D concentrations ( $<30$  ng/ml). Their ages ranged from 52 to 64 years with mean  $\pm$  SD of  $57.2 \pm 4.42$ . (33.8%) were married and (66.2%) were widowers. Their height ranged from 135 to 170 cm with median (IQR) of 160 (15). Their weight ranged from 59 to 130 kg with median (IQR) of 85 (28). Their BMI ranged from 32 to 47.7 with a median (IQR) of 33.2 (2.2) (Figure 1).

Table 2; there were no statistically significant differences between the groups in terms of demographic variables (age, BMI, parity, height, weight, marital status) or most clinical parameters ( $p > 0.05$ ), except for menopausal duration, which was significantly longer in Group I ( $p = 0.03$ ).

Tables (3) indicate that there were no significant differences between the two groups regarding psychological symptoms, urogenital symptoms, and menopause rating scale scores, as all P-values were greater than 0.05 ( $P > 0.05$ ).

Figure (2) showed statistically significant correlations between vitamin D levels and certain variables specifically, a positive correlation with age ( $r=0.238$ ,  $P<0.001$ ) and menopausal duration ( $r=0.304$ ,  $P<0.001$ ), and a negative correlation with BMI ( $r=-0.257$ ,  $P<0.001$ ) and MRS score ( $r=-0.178$ ,  $P=0.003$ ) these correlations are relatively weak

(correlation coefficients  $< 0.3$ ), suggesting limited strength of association.

To identify factors that independently affected MRS, multiple linear regression analysis was performed using age, height, weight, BMI, parity, menopausal duration and vitamin D as independent variables and MRS as dependent variable. MRS was negatively associated with age, menopausal duration and vitamin D ( $\beta = -0.098$ ,  $P=0.008$ ), ( $\beta = -0.204$ ,  $P<0.001$ ) and ( $\beta = -0.267$ ,  $P=0.003$ ) respectively,

independent of previously mentioned variables table 4.

Receiver Operating Characteristic (ROC) analysis showed that vitamin D levels had a fair predictive ability for severe menopausal symptoms. A cutoff point of 26.3 ng/mL yielded a sensitivity of 88.24% and specificity of 61.18%, with an area under the curve (AUC) of 0.798, indicating good diagnostic accuracy as shown in figure 3.

**Table 1:** Classification Of the Menopause Rate Scale severity

Severity	Score
None/little	0-4
Mild	5-8
Moderate	9-16
Severe/very severe	$\geq 17$

**Table (2):** Demographic data among the studied groups (n = 305)

Variables		Group I (n=98)	Group II (n=207)	P Value
<b>Age (years)</b>				
Mean $\pm$ SD		58 $\pm$ 4.41	57.2 $\pm$ 4.42	0.18 <sup>1</sup>
Range		(52 – 64)	(52 – 64)	
<b>Age groups (No., %)</b>				0.09 <sup>2</sup>
< 55 years		10 (10.2%)	41 (19.8%)	
< 60 years		51 (52%)	102 (49.3%)	
$\geq 60$ years		37 (37.8%)	64 (30.9%)	
<b>Marital status (No., %)</b>				0.84 <sup>3</sup>
Married		32 (32.7%)	70 (33.8%)	
Widow		66 (67.3%)	137 (66.2%)	
<b>Height (cm)</b>				0.81 <sup>4</sup>
Median (IQR)		164 (15)	160 (15)	
Range		(135 – 170)	(135 – 170)	
<b>Weight (Kg)</b>				0.49 <sup>4</sup>
Median (IQR)		89 (28)	85 (28)	
Range		(59 – 130)	(59 – 130)	
<b>BMI (Kg/m<sup>2</sup>)</b>				0.2 <sup>4</sup>
Median (IQR)		32.9 (2.2)	33.2 (2.2)	
Range		(32 – 47.7)	(32 – 47.7)	
<b>Parity</b>	Median (IQR)	5 (2)	5 (2)	0.53 <sup>1</sup>
	Range	(2 – 7)	(2 – 7)	
<b>Menopausal duration (years)</b>	Median (IQR)	13 (7)	10 (9)	0.03 <sup>1</sup>
	Range	(3 – 17)	(3 – 17)	
<b>Medical illness (n. %)</b>	DM + HTN	29 (29.6%)	73 (35.3%)	0.51 <sup>2</sup>
	HTN	18 (18.4%)	32 (15.5%)	
	Asthmatic	19 (19.4%)	32 (15.5%)	
	HTN + RBBB	13 (13.3%)	38 (18.4%)	
	Nil	19 (19.4%)	32 (15.5%)	

\*Student T test, <sup>2</sup>Fisher exact test, <sup>3</sup>Chi-square test, <sup>4</sup>Man-Whitney U test, Non-significant:  $P > 0.05$ , Significant:  $P \leq 0.05$  IQR: Interquartile range HTN: Hypertension RBBB: Right Bundle Branch Block

**Table (3):** Psychological, Urogenital Symptoms, and Menopause Rating Scale (MRS) Among the Studied Groups

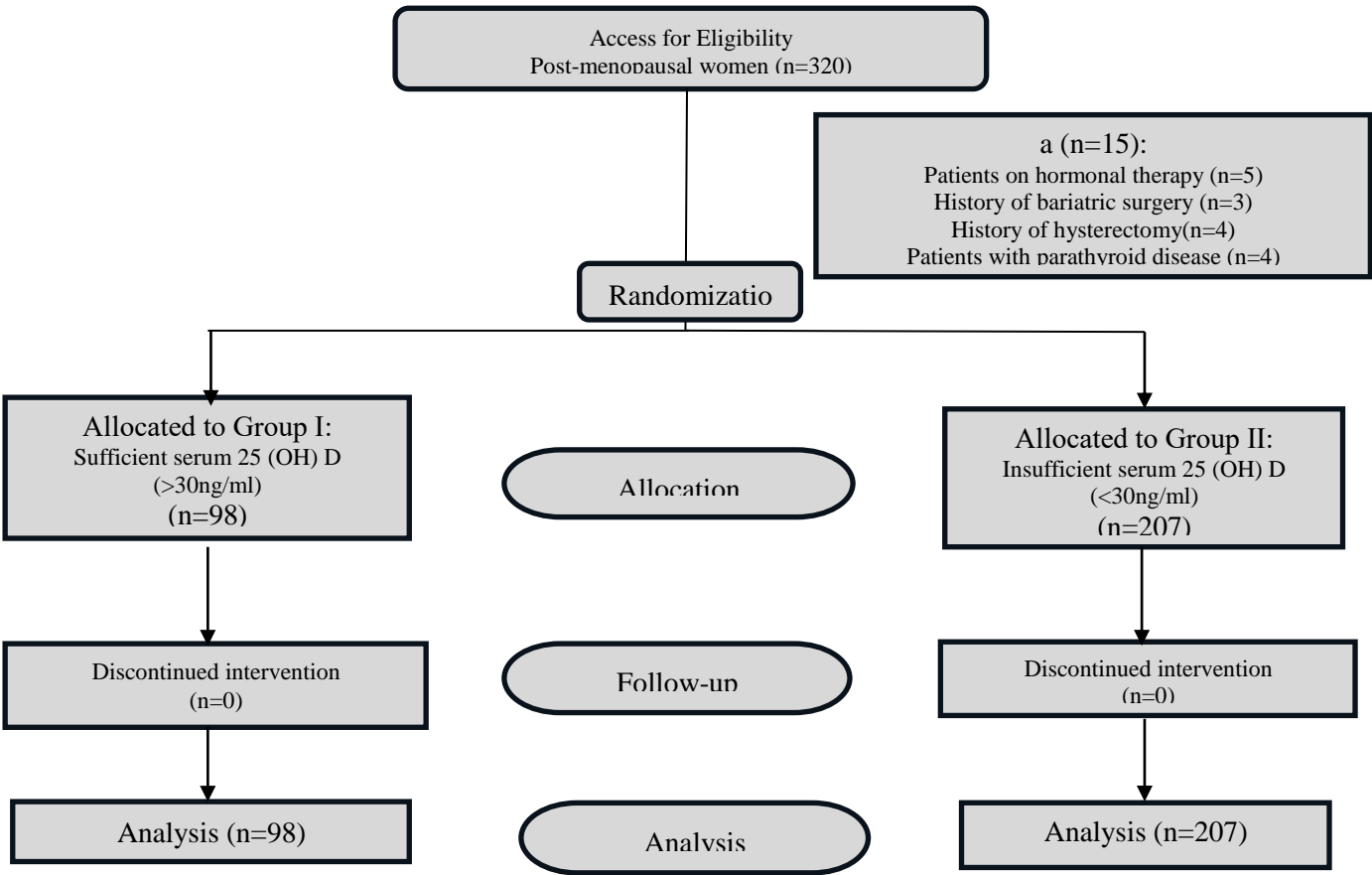
Variables (n. %)		Group I (n=98)	Group II (n=207)	P Value
<b>Psychological symptoms</b>				
<b>Depressed mood</b>	Nil	19 (19.4%)	32 (15.5%)	0.44 <sup>2</sup>
	Mild	51 (52%)	102 (49.3%)	
	Moderate	28 (28.6%)	73 (35.3%)	
<b>Irritability</b>	Mild	51 (52%)	102 (49.3%)	0.65 <sup>1</sup>
	Moderate	47 (48%)	105 (50.7%)	
<b>Anxiety</b>	Mild	38 (38.8%)	64 (30.9%)	0.17 <sup>1</sup>
	Moderate	60 (61.2%)	143 (69.1%)	
<b>Physical exhaustion</b>	Moderate	79 (80.6%)	175 (84.5%)	0.41 <sup>2</sup>
	Severe	19 (19.4%)	32 (15.5%)	
<b>Mental exhaustion</b>	Moderate	79 (80.6%)	175 (84.5%)	0.41 <sup>2</sup>
	Severe	19 (19.4%)	32 (15.5%)	
<b>Urogenital symptoms</b>				
<b>Sexual problems</b>	Nil	66 (67.3%)	137 (66.2%)	0.84 <sup>1</sup>
	Mild	32 (32.7%)	70 (33.8%)	
<b>Bladder problems</b>	Nil	18 (18.4%)	32 (15.5%)	0.57 <sup>2</sup>
	Mild	51 (52%)	102 (49.3%)	
	Moderate	29 (29.6%)	73 (35.3%)	
<b>Vaginal dryness</b>	Nil	38 (38.8%)	64 (30.9%)	0.17 <sup>1</sup>
	Mild	60 (61.2%)	143 (69.1%)	
<b>Menopause rating scale (MRS)</b>				
<b>Total MRS score</b>	Median (IQR)	16 (5)	17 (5)	0.51 <sup>1</sup>
	Range	(11 – 19)	(11 – 19)	
<b>MRS grade (n. %)</b>	Moderate	57 (58.2%)	96 (46.4%)	0.06 <sup>2</sup>
	Severe	41 (41.8%)	111 (53.6%)	

\*<sup>1</sup>Chi-square test, <sup>2</sup>Fisher exact test, Non-significant:  $P > 0.05$ , Significant:  $P \leq 0.05$

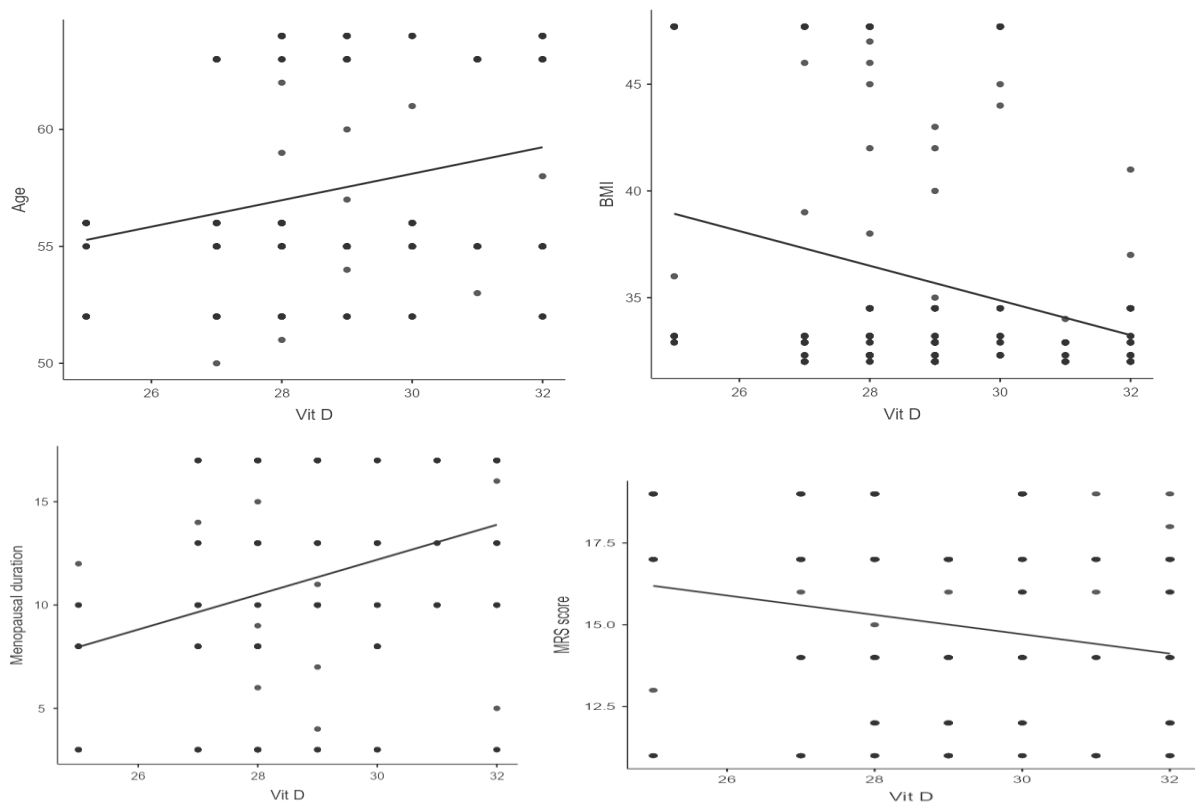
**Table (4):** multiple linear regression The analysis about severity of menopausal symptoms

Model fit measures	R=0.967	R <sup>2</sup> =0.935	P
Model coefficients	Estimate	t	
Age	-0.098	-2.69	0.008
Height	-0.019	-1.43	0.16
Weight	0.071	1.53	0.13
BMI	0.154	2.83	0.33
Parity	-0.154	-1.38	0.17
Menopausal duration	-0.204	-6.63	<0.001
Vitamin D	-0.267	-3.01	0.003

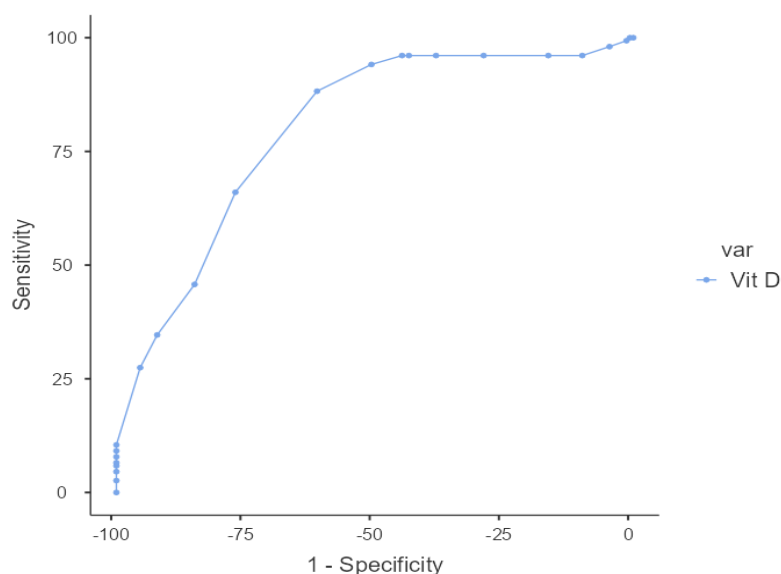




**Figure 1:** The study flowchart.



**Figure 2:** Scatter plots showing correlation between vitamin D and different parameters among the studied patients



**Figure 3:** ROC curve analysis of vitamin D to detect the severe scores of MRS among studied patients

### DISCUSSION

This study found no statistically significant differences between the two groups regarding demographic and clinical characteristics, except for menopausal duration, which was longer in Group I compared to Group II.

Hakim et al. [6] investigated the relationship between vitamin D levels and menopausal symptoms, reporting that 52.4% of their study population was vitamin D deficient. They found no significant differences in baseline characteristics between groups with sufficient and insufficient vitamin D levels.

Similarly, Erturk and Kender Erturk [7] explored the association between serum vitamin D levels and menopausal symptoms in women aged 42 to 65 years, with a mean age of 53.8 years. They reported that 38.1% of participants had vitamin D insufficiency (levels between 12 and 19 ng/mL), while 30 women had adequate levels ( $\geq 20$  ng/mL). No significant differences were observed in age, BMI, menopausal duration, or laboratory parameters between the groups.

Our study found no significant differences between the groups regarding musculoskeletal symptoms. Consistent with Hakim et al. [6], joint pain was the most prominent symptom on the Menopause Rating Scale (MRS) across both groups.

Similarly, no significant differences were observed between groups in terms of menopausal symptoms, urogenital complaints, or psychological symptoms measured by the MRS. Hakim et al. [6] also reported no significant differences between women with sufficient and

insufficient vitamin D levels, except for anxiety, which was higher in the vitamin D sufficient group. Both groups showed the highest MRS scores for muscle soreness and symptoms of anxiety and irritability. Additionally, urogenital, psychological, somato-vegetative, and overall menopausal symptom scores did not significantly differ between groups.

In contrast, Erturk and Kender Erturk [7] reported significantly higher total MRS scores in the vitamin D insufficiency group ( $22.97 \pm 2.71$ ) compared to others. They also observed increased somatic, psychological, and urogenital subscale scores among vitamin D deficient women. Post hoc analysis indicated that psychological symptom scores in the deficient group significantly differed from those in other groups. Both the insufficiency ( $n=38$ ) and deficiency groups ( $n=42$ ) showed significantly elevated urogenital subscale and total MRS scores compared to the sufficient group.

Assessments of anxiety, emotional and physical exhaustion, sexual problems, and vaginal dryness were similar across groups. However, other factors in the MRS questionnaire demonstrated significant differences between groups[7].

The association between anxiety and vitamin D remains inconsistent in the literature. Huang et al. [9] found no significant link, whereas Pu et al. [8] reported a positive correlation. These studies, however, investigated different populations such as pregnant women, pediatric dialysis patients, and individuals with rheumatoid arthritis. Furthermore, Foti et al. [10] found that lower

urinary tract symptoms were more prevalent in women with deficient vitamin D levels.

Vitamin D exerts a neuroprotective effect by preventing oxidative damage to brain cells. Meanwhile, decreased estrogen levels may impair central nervous system functions, affecting electrical excitability and synaptic transmission, potentially leading to increased anxiety[11].

Hakim et al. [6] reported no significant difference in menopausal symptom severity between women with sufficient and deficient vitamin D levels. Among women with moderate symptoms, nine had both adequate and deficient vitamin D levels. Additionally, 30 patients with moderate symptoms had insufficient vitamin D, while 27 had sufficient levels. For severe symptoms, 44 women had adequate vitamin D, compared to 49 with deficiency.

In our study, vitamin D levels correlated positively and significantly with age and menopausal duration, while showing a strong negative correlation with BMI and MRS scores. Similarly, Arvold et al. [12] found that severe vitamin D deficiency was associated with increased anxiety, depression, and reduced functioning in both men and women in a randomized controlled trial.

Tan et al. [13] reported that a BMI above 30 kg/m<sup>2</sup> was significantly associated with higher scores of depressive mood. Similarly, Erturk and Kender Erturk [7] found a negative correlation between vitamin D levels and Menopause Rating Scale scores.

A multiple linear regression analysis was performed using age, height, weight, BMI, parity, menopausal duration, and vitamin D as independent variables, with MRS score as the dependent variable. The results demonstrated that MRS was independently and inversely associated with age, menopausal duration, and vitamin D levels.

Hakim et al. [6] conducted a multivariable linear regression analysis to identify predictors of menopausal symptom severity. They reported that the presence of medical comorbidities was the strongest predictor; women with medical conditions had a 41% increased risk of experiencing severe menopausal symptoms compared to those without such conditions.

ROC curve analysis showed that a vitamin D level of 26.3 ng/mL provided the best balance of sensitivity (88.24%) and specificity (61.18%) for predicting severe menopausal symptoms, with an area under the curve (AUC) of 0.798. Similarly, Erturk and Kender Erturk [7] used ROC analysis for 25-OH vitamin D levels to identify severe MRS scores, reporting an AUC of 0.876. Their

cutoff value was 25.31 ng/mL, yielding sensitivity and specificity of 85.7% and 87%, respectively

When accounting for other patient characteristics, vitamin D levels did not independently predict the severity of menopausal symptoms but were associated with the presence of medical comorbidities. This finding aligns with LeBlanc et al. [14], who investigated the relationship between baseline serum 25(OH)D and menopausal symptoms and found no significant correlation. Their study assessed symptom severity based on the number of symptoms rather than using validated questionnaires. Moreover, their participants were older, with an average age of 66 years and a longer mean postmenopausal duration by approximately 10 years compared to our cohort. This difference might explain the lack of association found in their study.

Conversely, Martino et al. [15] reported a significant association between vitamin D levels and anxiety symptoms, independent of age or depression status.

Buell and Dawson-Hughes [16] highlighted the role of vitamin D in adult brain function and development. Vitamin D receptors and enzymes responsible for its activation are present in neurons, glial cells, and the pituitary gland, suggesting that vitamin D influences neurological and psychological processes.

Additionally, Van Schoor and Lips [17] reported a link between increased severity of menopausal symptoms and the presence of chronic illnesses, indicating that comorbid conditions may exacerbate menopausal symptom burden.

Hakim et al. [6] emphasized that vitamin D deficiency is a prevalent concern among postmenopausal women, although they found no direct association between vitamin D status and menopausal symptoms.

Erturk and Kender Erturk [7] suggested that low vitamin D levels during menopause might worsen menopausal symptoms, proposing that vitamin D supplementation could potentially benefit symptomatic women.

This study has several limitations that should be considered when interpreting the findings. First, although a multistage random sampling technique was employed, potential confounding factors such as sun exposure, dietary vitamin D intake, physical activity, and clothing habits which may significantly influence serum vitamin D levels were not assessed or controlled for. These unmeasured variables could have contributed to variations in vitamin D status and possibly affected the severity of menopausal symptoms. Second, due to the cross-sectional design, the study cannot establish causality



between vitamin D levels and menopausal symptoms; it can only demonstrate associations. Third, the study was conducted in a single center, which may limit the generalizability of the findings to broader populations. Lastly, although the Menopause Rating Scale (MRS) is a validated instrument, self-reported data may introduce reporting bias.

Despite these limitations, the study benefits from a relatively large sample size, clearly defined inclusion and exclusion criteria, and the use of standardized biochemical measurements to assess serum 25(OH)D levels, which enhances the reliability of the results.

### Conclusions

Although vitamin D deficiency remains a prevalent concern among postmenopausal women, our findings indicate a statistically significant negative association between vitamin D levels and the severity of menopausal symptoms. These results highlight the potential role of vitamin D in modulating symptom burden and underscore the need for further prospective studies to evaluate the benefits of vitamin D optimization in this population.

**Conflict of interest:** None.

**Financial Disclosures:** None.

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