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ORIGINAL ARTICLE

The Relationship Between Vitamin D levels and Severity of Menopausal Symptoms

Vitamin D ve Menopozal Semptomların Şiddeti Arasındaki İlişki

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ABSTRACT

Aim: Our aim was to investigate the relationship between menopausal symptoms and serum vitamin D levels.
Material-Method: We analyzed 110 postmenopausal women aged between 42-65 years among menopause symptoms by using Menopause Rating Scale (MRS) questionnaire. Patients were divided into three groups according to their serum 25-OH vitamin D levels; sufficient (>20 ng/mL), insufficient (12-20 ng/mL), deficient (<12 ng/mL), then compared. Serum vitamin D cut-off level was determined for menopausal symptoms. The correlations between symptoms and vitamin D status were calculated.
Results: Vitamin D deficiency was detected in 38,1% (42/110) of the participants. The total MRS score was 22,97±2,71 in Vitamin D deficiency group and significantly higher than others (p<0,001). In deficiency group, somatic, psyhcological and urogenital subscale scores were higher than other groups (p<0,001, p=0,007 and p=0,036, respectively). Evaluation of the correlations among independent variables revealed a negative relationship between vitamin D level and MRS scores. The threshold value at which serum vitamin D causes severe MRS scores in those with sufficient levels was calculated as 25.31 ng/ml. The area under the ROC curve was 0,876 (95% CI, 0,702-1,00, p=0.003).
Conclusion: In the present study, a relationship between serum vitamin D levels and menopause-related symptoms in postmenopausal population was demonstrated. Low levels of vitamin D in menopausal period might aggravate menopause-related symptoms.
Keywords: Menopause-related symptoms, vitamin D, postmenopausal

ÖZ

Amaç: Amacımız menopoz semptomları ile serum D vitamini düzeyleri arasındaki ilişkiyi araştırmaktı.
Gereç-Yöntem: Menopoz semptomları, 42-65 yaş arası 110 postmenopozal kadında Menopoz Derecelendirme Ölçeği (MDÖ) anketi kullanılarak analiz edildi. Hastalar serum 25-OH D vitamini düzeylerine göre üç gruba ayrıldı; yeterli (>20 ng/mL), azalmış (12-20 ng/mL), eksik (<12 ng/mL), sonra karşılaştırıldı. Şiddetli menopoz semptomlarına yol açan serum D vitamini düzeyi için ROc eğirisi ile eşik değer belirlendi. Semptomlar ve vitamin D seviyesi arasındaki korelasyon hesaplandı.
Bulgular: Katılımcıların %38,1'inde (42/110) D vitamini eksikliği saptandı. D vitamini eksikliği grubunda toplam MDÖ puanı 22,97±2,71 olup diğerlerinden anlamlı olarak yüksekti (p<0,001). Eksiklik grubunda somatik, psikolojik ve ürogenital alt ölçek puanları diğer gruplara göre daha yüksekti (sırasıyla p<0,001, p=0,007 ve p=0,036). Bağımsız değişkenler arasındaki korelasyonlar değerlendirildiğinde, D vitamini düzeyi ile MDÖ puanları arasında negatif bir ilişki ortaya çıktı. Yeterli düzeyde olanlarda serum D vitamininin ciddi MDÖ skorlarına neden olduğu eşik değer 25.31 ng/ml olarak hesaplandı. ROC eğrisi altında kalan alan 0,876 (%95 CI, 0,702-1,00, p=0,003) idi.
Sonuç: Bu çalışmada postmenopozal popülasyonda serum D vitamini düzeyleri ile menopoza bağlı semptomlar arasında ilişki olduğu gösterilmiştir. Menopoz dönemindeki düşük D vitamini seviyeleri menopoza bağlı semptomları şiddetlendirebilir.

Anahtar Kelimeler: Menopozla ilişkili semptomlar, Postmenopozal, Vitamin D

Introduction

Natural menopause is defined as the absence of menstruation for one year in women without any other underlying causes. In the menopausal period, low estrogen and high follicle stimulating hormone (FSH) concentrations are observed due to the decrease or disappearance of ovarian follicles (1). This hormonal instability in menopausal period may cause a number of physical and psychological complaints such as vasomotor symptoms, genito-urinary symptoms, mood and sleep disturbance(2). These menopause-related symptoms can negatively affect the individual's quality of life, work life and personal relations (3).

Vitamin D is a fat-soluble vitamin that has important roles in calcium metabolism and musculoskeletal system. In addition to its role in calcium and bone homeostasis, vitamin D potentially regulates many other cellular functions. In this regard Vitamin D deficiency can cause many infectious, autoimmune and cardiovascular diseases(4). It was also shown that Vitamin D has a protective impact againsts cardiovascular risks in women (5). In addition, there are several data showing that there may be a relationship between vitamin d deficiency and hot flushes, irritability and genitourinary sypmtoms(6–8). Arvold et al showed a correlation of severe vitamin D deficiency with anxiety, depression and impaired functionning in their randomized control trial in men and women population(9).

Given this background, it could be understood that the symptoms seen in vitamin D deficiency coincide with the symptoms seen in women during menopause. Therefore, we aimed to investigate whether there is a relationship between vitamin D levels and menopause-

related symptoms in postmenopausal women.

Material and Methods

This cross-sectional study consisted of 110 postmenopausal women who applied for routine gynecological examination to a tertiary center gynecology clinic. After obtaining the local ethical approval and written informed consent of each patient, demographic characteristics, medical histories, physical and gnynecological examination findings including body mass index (BMI), time since menopause of subjects were recorded. Menopause was defined as not having menstruel bleeding more than a year. Patients' serum follicule stimulating hormone (FSH), estradiol (E2), calcium (Ca), 25-OH vitamin D levels were measured.

Menopausal symptoms of all patients were evaluated using Meopause Rating Scale (MRS) questionnaire validated for Turkish-speaking populations (10). The MRS includes 11 items assigning a score of 0-4 for the severity of the symptom (0, absent; 1, mild; 2, moderate; 3, severe; 4, very severe). This questionnaire is divided into three domains; somatic subscale including hot flushes, heart discomfort, sleep problems, muscle and joint discomfort (items 1-3,11); psychological subscale including depressive mood, irritability, anxiety, physical and mental exhaustion (items 4-7); urogenital subscale including sexual problems, bladder problems, vaginal dryness (items 8-10). Total MRS score is the sum of the scores obtained in each subscale. The values above 8 for somatic score, 6 for psychological score, 3 for urogenital score and 16 for total MRS score were defined as severe scores (11).

The study included postmenopausal women aged between 40-65 years. Patients using hormon replacement therapy (HRT), with systemic diseases and medical conditions associated with vitamin D deficiency, taking any supplemental medications, smoking, with surgical menopause were excluded from study.

The subjects were divided into three groups according to their serum 25-OH vitamin D levels; sufficient (>20 ng/mL), insufficient (12-20 ng/mL), deficient (<12 ng/mL) (12) and then compared among the parameters mentioned.

Data were analyzed by SPSS 21.0 for Windows (SPSS Inc, Chicago, IL, USA) statistics programme. The normality of distribution was assessed by Shapiro-Wilk test. Analysis of variance (ANOVA) and Kruskall-Wallis tests were used for analysis of continuous variables. Post-Hoc analysis was performed. Spearman rho coefficients were calculated for correlation analysis. The ROC curve was plotted for vitamin D level associated with severity of menopausal symptoms. P<0.05 was considered statistically significant.

Results

The mean age of the patients was 53,8 years (range, 42 to 65 years). Mean time since menopause for patients was 6,1 years (range, 1 to 20 years). Vitamin D deficiency was detected in 38,1% (42/110) of the participants. Serum 25-OH Vitamin D levels of 30 women were ≥20 ng/mL, sufficient. The Vitamin D levels of the remaining 38 patients were insufficient, between 12-19 ng/mL. There were no differences among age, BMI, time since menopause and laboratory characterictics between groups (Table 1).

The total MRS score was 22,97±2,71 in Vitamin D deficiency group and significantly higher than others (p=0,001) (Table 1). Besides that, in deficiency group, somatic, psyhcological and urogenital subscale scores were higher than other groups (p=0,012, p=0,007 and p=0,036, respectively)(Table 1). According to post-hoc analysis, psychological scores of the deficiency group (8,02±2,87 and 9,42±5,15) were significantly different from the other groups. Urogenital subcale and total scores of deficiency group (n=42) were similar to insufficiency group (n=38), significantly higher than sufficieny group (Table 1).

Anxiety, physical and mental exhaution, sexual problems and dryness of vagina scores of patients were similar between groups. Besides that, there were significantly differences among groups according to the remaining parameters of MRS questionnaire (Table 2).

Evaluation of the correlations among independent variables revealed a negative relationship between vitamin D level and MRS scores (Table 3).

The ROC curve for 25-OH vitamin D to detect the severe scores of MRS in women with sufficient vitamin D level in Figure 1. The area under the ROC curve was 0,876 (95% CI, 0,702-1,00, p=0.003) for vitamin D. The cut-off value of serum vitamin D level was 25,31 ng/ml, at which the sensitivity was 85,7% and specificity was 87%.

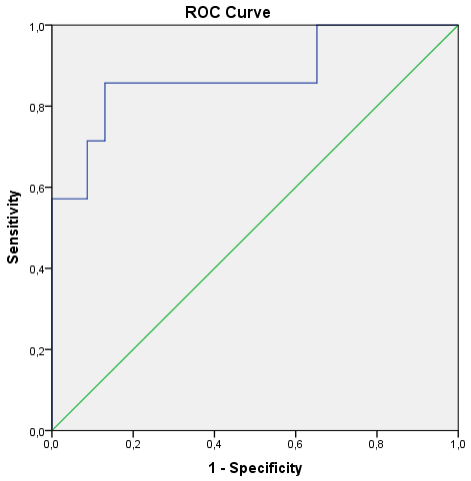

Figure 1. Receiver operating characteristic (ROC) curve for serum 25-OH Vitamin D level The estimate of the area under curve (AUC) and its 95% confidence interval is shown. Cut-off value of vitamin D was 25,31 (sensitivity 85,7 % and specificity 87%). AUC, area under curve. $p < 0.05$ was considered significant .

Table 1. Demographic, laboratory characteristics and rating scores of the subjects among groups.

	25-OH vitamin D levels			
	≥20 ng/mL n=30	12-19 ng/mL n=38	<12 ng/mL n=42	*p*
Age (y)	53,20±4,98	53,50±4,43	54,71±3,94	NS
BMI (kg/m^2)	30,00±5,00	30,04±4,27	30,66±4,84	NS
Time since menopause (y)	5,50±4,03	6,38±5,68	6,98±4,99	NS
Serum FSH (mIU/mL)	65,00±23,78	62,29±19,82	63,28±20,74	NS
Serum E_2 (pg/mL)	18,47±15,99	20,09±12,18	16,56±10,90	NS
Serum Ca (mg/dL)	9,76±0,35	9,63±0,42	9,62±0,40	NS
Somatic subscale score	4,33±2,42	6,39±2,94	8,02±2,87	<0,001
Psychological subscale score	6,46±3,10	7,07±3,73	9,42±5,15*	0,007
Urogenital subscale score	3,90±2,02	5,23±3,09	5,52±2,71**	0,036
Total MRS score	14,73±5,93	18,71±7,55	22,97±2,71**	<0,001

y: years, BMI: body mass index, kg: kilogram, m:meter, FSH: Follicule stimulating hormone, E2: estradiol, Ca: calcium, MRS: Menopause reting scale, NS: non-significant.

*Statistical difference arises from group 1 and 2.

** Statistical difference arises from group 1.

p <0.05 was considered significant.

Table 2. Results of Menopause Rating Scale parameters among serum 25-OH Vitamin D levels.

Parameters	25-OH vitamin D levels			
	≥20 ng/mL n=30	12-19 ng/mL n=38	<12 ng/mL n=42	*p*
Hot flushes	1,26±1,11	1,86±0,99	2,30±1,02	<0,001
Heart discomfort	0,40±0,56	1,00±0,95	1,50±1,01	<0,001
Sleep problems	1,20±1,09	1,34±1,23	1,83±1,05	0,043
Depressive mood	1,53±1,04	1,57±1,13	2,30±1,07	0,003
Irritability	1,53±1,07	1,76±1,19	2,38±1,16	0,006
Anxiety	1,36±1,03	1,81±1,13	2,83±4,88	NS
Physical and mental exhaustion	2,03±1,21	1,92±1,26	1,90±1,07	NS
Sexual problems	1,56±0,93	1,97±1,28	1,73±1,38	NS
Bladder problems	1,10±1,09	1,60±1,28	2,09±1,22	0,040
Dryness of vagina	1,23±1,04	1,65±1,32	1,69±1,17	NS
Joint and muscular discomfort	1,46±1,10	2,18±1,20	2,38±1,24	0,006

NS: non-significant *p* <0.05 was considered significant.

Table 3. Correlations among variables.

	r	p
Vitamin D- SSS	-0,469	<0,001
Vitamin D- PSS	-0,295	0,002
Vitamin D- USS	-0,251	0,008
Vitamin D- Total MRSS	-0,432	<0,001

SSS: Somatic subscale score, PSS:Psycholocigal subscale score, USS: Urogenital subscale score, MRSS: Menopause rating scale score, r: correlation coefficient. *p* <0.05 was considered significant.

Discussion

In the present study, we demonstrated a relationship between serum vitamin D levels and menopause-related symptoms in postmenopausal population. We were able to show a significant negative correlation between vitamin D levels and MRS total/subscale scores. Our results also represented that symptoms such as hot flushes, heart discomfort, depressive mood, irritability, bladder problems and joint and muscular discomfort in postmenopausal period were significantly severe in women with vitamin D deficiency. We also calculated a 25-OH vitamin D cut-off for women complaining from menopause-related symptoms despite having sufficient vitamin D levels.

In a study reported in 2014, LeBlanc et al. could not find an association between menopausal symptoms and serum vitamin D levels (13). In their study, they identified some menopausal symptoms, then participants rated these symptoms according to intensity of the symptom. A total score was defined as the total number of symptoms of any severity. So unlike ours, any validated questionnaire were not used in that study. Besides that, their subjects were older (66 years) and the mean time since menopause in the mentioned study was about ten years higher than our study. The reason they failed to report any association between vitamin D levels and menopausal symptoms could be explained by the high number of women with menopause duration of more than ten years.

Vitamin D taken in diet or synthesized in the skin is biologically inactive and requires enzymatic conversion to active metabolites. It was shown that estrogen plays a role in the increase of vitamin D activating enzyme (14). Therefore, it could be thought that the decrease of estrogen levels in postmenopausal period might worsen the symptoms of subclinical vitamin D deficiency such as neuropsychiatric symptoms. There are few data evaluating the neuroprotective role of vitamin D. An experimental study investigating the effect of menopause on behavioral status found that menopause could cause an impairment in memory (15). Siebert et al showed that vitamin D supplementation reverses the hippocampal cytoskeletal changes caused by ovariectomy, in vivo. In another animal

testing, increasing calcidiol levels by vitamin D supplementation in ovariectomized rats was reported to reduce the hippocampal inflammatory mediators such as nuclear factor-kappa B and interleukin-6(16). Besides the hippocampal effects, cholecalciferol was concluded as an anxiolytic agent in ovariectomized rats (17). It could be seen that these data support the psychological outcome in our study. Depressive mood and irritability scores of the subjects were significantly higher in the deficiency group. Furthermore, anxiety score was also higher in this group although it was not statistically significant. Evaluating the total psychiatric score, a significant difference had been already encountered in the deficiency group. Similarly, in a report with a high patient population discoursing vitamin D and symptoms in menopause, it was mentioned that 25-OH vitamin D levels were low and depression scores were high in the postmenopausal period (18).

Although psychological score differed significantly among patient groups, this score was severe, higher than six, in all groups. The severity of this score might be due to our patients' high BMIs. In a cross-sectional study from Turkey using MRS, Tan et al. reported that BMI higher than 30 kg/m2 was signifacntly associated with higher depressive mood score (19).

Another finding in our study was the high scores of urogenital subscale in the insufficiency and deficiency groups. In this subscale especially bladder problems section score was noticed as significantly high. Considering the literature, it was seen that low urinary tract symptoms could be associated with serum vitamin D levels. Because pelvic floor muscle strength might be affected by low vitamin d levels. In a study including both patients in pre and postmenopausal periods, pelvic floor muscle strength was calculated lower in postmenopausal patients with vitamin D levels lower than 20 ng/mL (20). In the same study, it was reported that urinary incontinence score was higher in women with vitamin D deficiency, but they could not find statistical difference (20). Unlike that study, our results about the vitamin D levels and urinary system symptoms were statistically significant. Similiarly, Foti et al concluded that prevelance of low urinary tract symptoms was significantly higher in women with low vitamin D levels comparison to those with normal levels (8). Moreover, the siginificant improvement of lower urinary symptoms in postmenopausal patients treated with high dose vitamin D for one year was documented in a randomized controlled trial published in 2017 (21).

Somatic symptoms like hot flashes could often be challenging for menopausal women. Regardless of vitamin D levels, most of the women complain about these symptoms (22). In our study, we found a negative correlation between somatic scores and vitamin D levels. Vitamin D was described to prevent seratonin depletion in rats (6). Seratonin was known as a neurotransmitter playing role in thermoregulation, a decline seratonin levels might cause hot flashes(7). In this context, high levels of vitamin D might protect against somatic symptoms, especially hot flashes, during menopause. In addition, in a recent study, it was mentioned that menopausal symptoms are less common in women with normal vitamin D levels than in women with vitamin D deficiency (23).

In this study, we hoped to clarify whether vitamin D deficiency caused spesific menopause-related symptoms. In this regard, we used a validated questionnaire-MRS, tried to minimized external factor that could affect scale rates by excluding patients with any other comorbidities. Our patient groups were similar among demographic and hormonal characteristics. Besides that, we presented a cut-off 25-OH vitamin D level for women suffering from menopause releated symptoms with sufficient levels of vitamin D. Unlike the literature, time since menopause in our patients was short. Apart from these strengths, the study had limitations. Our patient population consisted of one geographic area. We could not able to evaluate the parathormone levels of the patients and we could not distinguish whether menopause-related symptoms associated with vitamin D deficieny would change when treated with supplementation.

In conclusion, low levels of vitamin D in menopausal period might aggravate menopause-related symptoms. It could be considered that menopausal women with a high intensity of symptoms might benefit from vitamin D supplementation. Further prospective studies are needed to clearly enlighten this complex and multicomponent relationship.

Conflict of interests : The authors declare no conflict of interests

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