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Is There a Role of 25-Hydroxy Vitamin D in the Pathogenesis of Mild and Moderate-to-Severe Endometriosis?

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ABSTRACT

OBJECTIVE: To evaluate the possible associations between serum 25-hydroxy vitamin D levels and clinical and laboratory parameters in endometriosis.

STUDY DESIGN: A total of 53 women with endometriosis and 37 women without endometriosis were evaluated in a, case-controlled study. The demographic features, clinical, and laboratory parameters of the two groups were compared.

RESULTS: The serum 25-hydroxy vitamin D levels were significantly decreased in both stage 1-2 and stage 3-4 groups compared to the controls (p<0.001 and p<0.001); although the difference between the stage 1-2 and stage 3-4 groups remained nonsignificant. The serum 25-hydroxy vitamin D levels had no correlation with the presence of infertility, deep infiltrating endometriosis, or Douglas pouch obliteration. The women who had bilateral endometrioma had significantly lower levels of 25-hydroxy vitamin D compared to the women with unilateral endometrioma (8.4±2.7 ng/mL vs 11.1±5.6 ng/mL, p=0.047). Mean serum 25-hydroxy vitamin D levels in women with and without dysmenorrhea were not significantly different from each other in the endometriosis and non-endometriosis subgroups. Serum 25-hydroxy vitamin D had no correlation with dysmenorrhea-VAS scores (r=-0.157, p=0.267).

CONCLUSION: The mean serum 25-hydroxy vitamin D levels were significantly decreased in both mild and moderate to severe endometriosis groups compared to the controls. The serum 25-hydroxy vitamin D levels had no correlation with the presence of infertility, deep infiltrating endometriosis, or Douglas pouch obliteration. The women who had bilateral endometrioma had significantly lower levels of 25-hydroxy vitamin D compared to the women with unilateral endometrioma.

Keywords: 25-hydroxy vitamin D, Dysmenorrhea, Endometrioma, Endometriosis, Vitamin D

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Introduction

Endometriosis is a common cause of infertility and pelvic pain and affects more than 10% of the women in reproductive age (1,2).

It may mimic some autoimmune and even malignant diseases, including immunological aberrations in lymphocytes, neoangiogenesis, and endometrial tissue invasion to the neighbor organs (1,3-5). A number of recent studies have shown that inflammatory, immunological, genetic, and environmental factors play a role in the pathogenesis of endometriosis. The factors that influence the inflammatory cascade or immune system may also influence the development of endometriosis. As a matter of fact, a malfunction somewhere in the immune system is probably responsible for a state of chronic inflammation, which contributes to the development or worsening of endometriosis (6).

In addition to the reduction in T-cell cytotoxicity, endometriosis is associated with a functional inadequacy of the natural killer (NK) cells and a greater number of activated macrophages in the peritoneal fluid. The overactivation of the

macrophages triggers an avalanche of cytokines and angiogenesis factors (7,8). In accordance with this hypothesis, an increase in inflammatory cytokines has been shown in the peritoneal fluid and serum of women with endometriosis (9).

Possible associations between serum vitamin D and the risk of various gynecological disorders such as polycystic ovarian syndrome, and mammary carcinoma and ovarian carcinoma have also been suggested.

Vitamin D plays a role in the regulation of normal cell growth as well as immune regulatory effects in chronic inflammatory responses (10,11). It increases the production of anti-inflammatory cytokines as it decreases proinflammatory cytokines (10-13). Moreover, it is also known to induce programmed cell death and suppression of neovascularization (14-17).

In our study, we aimed to evaluate the possible associations between serum 25-hydroxy vitamin D (25-OH-D) levels and clinical and laboratory parameters in endometriosis.

Material and method

A total of 53 women with endometriosis, who was diagnosed at Istanbul University, Cerrahpasa School of Medicine Hospital between May 2012 and July 2013, and 37 women without endometriosis were evaluated in a case-controlled study. Informed consent was obtained from all women. The study was approved by the Istanbul University, Cerrahpasa School of Medicine Ethics Committee (#01/10/2012-5749 and #5/12/2018-104542). Our study protocol was in accordance with the ethical standards for human experimentation established in the Declaration of Helsinki.

Inclusion criteria for the study group were women, between 15 and 40 years old, who have histologically proven endometriosis.

Exclusion criteria included recent vitamin D intake (in the last six months prior to surgery), current use of UV tanning lamps, any systemic diseases, known malignancy, menopause, and hormone replacement or treatment such as oral contraceptives. The control group included 37 consecutive women undergoing diagnostic laparoscopy due to infertility and did not have any macroscopic endometriotic lesion.

The laparoscopy indications included ovarian cyst, infertility, pelvic pain conditions such as menstrual or non-menstrual pelvic pain and pain during coitus or defecation. The endometriosis was diagnosed histologically by the samples taken during laparoscopy. On admission, the demographic and clinical data such as age, body mass index (BMI) and obstetrical history were recorded, and the visual analog scale (VAS) score was calculated for each woman for the severity of pelvic pain and dysmenorrhea. A VAS score of 0 indicated the absence of pain while a VAS score of 10 indicated the highest point of pain.

A mini-questionnaire about the current and previous sun exposure habits had been performed to more or less standardize the women participating in the study. The amount of sun exposure during work and leisure as well as the use of protective tanning cream were questioned. The answers were evaluated and scored.

The revised American Society for Reproductive Medicine (ASRM) classification was considered during the evaluation of the severity of endometriosis (18). The severity stages were classified under two subgroups as mild (stage 1 and 2) (n=28) and moderate/severe (stage 3 and 4) (n=25) endometriosis.

Samples were obtained just before the operation. 5–10 ml of venous blood samples were collected using a peripheral venous catheter (PVC). In order to allow clotting, the blood samples were kept at room temperature for at least 30 minutes. The serum supernatants were separated following centrifugation at 5000 g for 10 min then stored at 80 ^{o}C until analyses. C-reactive protein (CRP) and white blood cell count (WBC), CA125, parathormone, calcium, phosphorus, and 25-OH-D levels were measured. The quantitative measurement of 25-OH-D was performed using chemiluminescent immunoassay (CLIA) technology with the DiaSorin Liaison 25(OH)D TOTAL assay (DiaSorin, USA). Parathormone and CA125 were measured with the electrochemiluminescence technique. Alkaline phosphatase was measured with the photometric technique.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) software version 18.0 was used for database formation and statistical analyses. Parametric data were shown as mean ± standard deviation (SD). The comparison of the parametric variables between the groups was made using the T-test or ANOVA. The Pearson correlation test was used to evaluate the possible correlations between the parametric variables. A p value less than 0.05 was accepted as statistically significant.

Results

The clinical, demographic and laboratory features of 53 women with endometriosis and 37 women without endometriosis were shown in table I. No significant differences were found between the groups regarding demographic parameters and obstetrical history. Rate of dysmenorrhea was significantly higher in the endometriosis group (p=0.003). The serum CRP and WBC levels were comparable between the groups. The serum CA 125 was significantly elevated in women with endometriosis compared to the controls (p=0.001).

Clinical and demographic features of the mild and moderate-to-severe endometriosis and the non-endometriosis groups were given in table II. The serum CRP and WBC levels were comparable between the latter groups. Serum CA 125 was significantly elevated in the mild endometriosis group compared to the controls (p<0.001). 25-OH-D levels were significantly

decreased in both mild and moderate-to-severe endometriosis groups compared to the controls (p<0.001 and p<0.001); although the difference between the mild and moderate-to-severe endometriosis groups remained nonsignificant (p=0.290).

Sixty percent of endometriomas were located in one ovary, and the rest of the patients had endometriomas on both ovaries. Douglas pouch obliteration was not detected in 25 (50.9%) women, whereas nine (16.9%) and 17 (32%) women had a partial and complete obliteration, consecutively. Peritoneal endometriosis rate was 35.8% and the rate of deep infiltrating endometriosis was 24.5%. The 25-OH-D levels had no correlation with the presence of infertility, deep infiltrating endometriosis, or Douglas pouch obliteration. The women who had bilateral endometrioma had significantly lower levels of 25-OH-D compared to the women with unilateral endometrioma (8.4±2.7 ng/mL vs 11.1±5.6 ng/mL, p=0.047).

Mean serum 25-OH-D levels in women with and without dysmenorrhea were not significantly different from each other in the endometriosis and non-endometriosis subgroups (Table III). Serum 25-OH-D had no correlation with dysmenorrhea-VAS scores (r=-0.157, p=0.267).

Table I: *Demographic and laboratory features of endometriosis and non-endometriosis groups*

	Endometriosis (n=53)	Control-Group (n=37)	*p*
Age (years)	32.0±8.0	30.7±7.8	0.459
BMI (kg/m²)	24.0±4.5	24.7±4.6	0.464
Gravidity (n)	0.9±1.4	1.3±1.6	0.218
Parity (n)	0.5± 0.8	0.9±1.1	0.114
Duration of infertility (months)	69.5±56.5	120.4±122.1	0.176
Ca12.5 (U/mL)	81.1±66.3	15.8±7.0	**<0.001**
CRP (mg/L)	3.8±4.4	2.3±2.2	0.057
Leukocyte (n/mL)	7336±1616	6743±1632	0.093
Left shift	60.5±8.9	60.3±9.0	0.896
Parathormone (pg/mL)	51.0±11.2	49.6±6.5	0.475
25 OH-Vitamin D (ng/mL)	10.1± 4.8	19.3±7.8	**<0.001**
Alkaline phosphatase (U/L)	63.2±12.5	60.4±9.7	0.251
Calcium (mg/dL)	9.2±0.39	9.1±0.2	0.564
Phosphorus (mg/dL)	3.2±0.5	3.2±0.4	0.745

BMI, body mass index; CRP, C-reactive protein, p < 0.05 is significant

Table II. *Demographic and laboratory features of stage 1-2, stage 3-4 endometriosis and non-endometriosis subgroups*

	Stage 1-2 Endometriosis (n=28)	Stage 3-4 Endometriosis (n=25)	Control-Group (n=37)	*p*1 (control-stage 1-2)	*p*2 (Stage 1-2 vs stage 3-4)
Age (years)	31.3±7.8	32.8±8.3	31.3±7.8	0.772	0.510
BMI (kg/m²)	22.9±3.7	25.2±5.1	24.7±4.6	0.119	0.100
Gravidity (n)	0.7±1.3	1.1±1.5	1.3±1.6	0.144	0.380
Parity (n)	0.5±0.8	0.6±0.8	0.9±1.1	0.103	0.528
Duration of infertility (months)	40.0±31.0	103.2±62.0	120.4±122.1	0.091	0.024
Dysmenorrhea	4.0±1.4	4.9±1.4	-	N/A	**0.039**
Ca12.5 (U/mL)	92.5±73.9	72.3±59.6	15.8±7.0	**<0.001**	0.301
CRP (mg/L)	3.0±3.2	4.7±5.3	2.3±2.2	0.339	0.177
Leukocyte (n/mL)	7435±1600	6990±1545	6743±1632	0.057	0.083
Left shift	61.1±8.8	59.9±9.2	60.3±9.0	0.638	0.719
Parathormone (pg/mL)	50.1±7.1	52.0±14.6	49.6±6.5	0.789	0.547
25 OH-Vitamin D (ng/mL)	10.7±5.08	9.3±4.5	19.3±7.8	<0.001	0.290
Alkaline phosphatase (U/L)	61.2±12.8	65.3±12.0	60.4±9.7	0.777	0.242
Calcium (mg/dL)	9.3±0.4	9.1±0.3	9.1±0.2	0.102	0.060
Phosphorus (mg/dL)	3.1±0.4	3.2±0.5	3.2±0.4	0.639	0.746

BMI: Body mass index, CRP: C-reactive protein, p<0.05 is significant

Table III: *Comparison of the vitamin D levels according to clinical features*

	Serum Vitamin D level (ng/mL) Mean ± SD	*p*
Infertility		
• Present (n=24)	14.4±8.2	0.070α
• Absent (n=66)	13.7±7.5	
Deep infiltrating endometriosis		
• Present (n=13)	9.2±5.0	0.316α
• Absent (n=40)	10.6±4.7	
Ovarian involvement		
• One ovary (n=32)	11.1±5.6	0.047α
• Two ovaries (n=21)	8.4±2.7	
Douglas obliteration		
• Absent (n=27)	10.9±5.03	
• Partial (n=19)	8.9±2.4	0.402β
• Total (n=9)	9.8±7.2	
Dysmenorrhea (in Endometriosis Group)		
• Absent (n=19)	11.6±5.8	0.135α
• Present (n=34)	9.2±4.0	
Dysmenorrhea (in Non-endometriosis Group)		
• Absent (n=25)	18.3±8.0	0.250α
• Present (n=12)	21.5±7.1	

α: *T-Test,* β: *One-Way ANOVA, p<0.05*

Discussion

In our study, the serum 25-OH-D levels were significantly decreased in both mild (stage 1-2) and moderate-to-severe (stage 3-4) endometriosis groups compared to the controls. There was no significant difference in the serum 25-OH-D levels between the mild and moderate-to-severe endometriosis groups.

The majority of the studies in the literature about vitamin D and endometriosis have shown that higher 1,25-OH vitamin D3 levels in circulation and increased consumption of milk products were suggested to be associated with a reduction in endometriosis risk (19,20). In their systematic review, Parazzini et al. concluded that endometriosis was associated with low dietary intake of vegetables and omega 3 (21).

Hwang et al. compared 13 ectopic- and six normal-endometrial tissues and have shown that the vitamin D binding protein (VDBP) was significantly increased in the ectopic endometrium (22). A systematic review by Sayegh et al. of 87 articles on vitamin D and endometriosis reported that serum levels VDBP levels were higher in women with endometriosis (23). Faserl et al. evaluated a possible correlation between VDBP and endometriosis and concluded that the concentration of VDBP was higher in all endometriosis patients compared to the control group (24). They suggested the possible involvement of polymorphism in the VDBP (GC-2) in the pathogenesis of endometriosis. The GC-2 polymorphism is seen more commonly in women with endometriosis. GC-2 polymorphism may be associated with inadequate activation of phagocytosis of macrophages, which in turn may lead to the failure of prevention of endometriotic tissue implantation on the peritoneum. Agic et al. have shown that VDR and 1α-hydroxylase expression in endometriosis specimen was significantly higher than in healthy tissues; however, 25-OH-D3 levels were comparable (5).

However, there are also contradictory findings in the literature. Somigliana et al. have suggested that women with endometriosis had an increased serum level of 25-OH-D3, compared to the control group, and this difference was statistically significant (25). The concentration of 1α,25-(OH)2D3 was also higher in the endometriosis group, but the difference was not statistically significant. However, 10 years later from the same center, Bugglio et al. detected that the 25-OH-D3 levels were comparable in women with and without endometriosis (26). Nevertheless, these findings contradict the findings from the studies, which suggest that high dietary intake of vitamin D reduces the risk of endometriosis development. High VDBP concentration both in serum and endometriotic tissue in women with endometriosis may be interpreted as increased need for vitamin D. Agic et al. have shown that the conversion of vitamin D to its active form was accelerated in endometriotic tissue, and its receptor production was increased (5). In our study, in accordance with these findings, serum 25-OH-D levels were decreased in women with endometriosis.

Miyashita et al. suggested that the level of vitamin D was found to be dependent on the degree of severity of endometriosis (27). In our study, the 25-OH-D levels had no correlation with the presence of infertility, deep infiltrating endometriosis, or Douglas pouch obliteration. Regarding the stage 1-2 and stage 3-4 groups, there was no significant difference in our study population. For that reason, according to our results, 25-OH-D cannot be considered as a severity marker.

Vitamin D intake is also known to be associated with pain reduction, which may be the result of decreased synthesis and increased inactivation of prostaglandins (PG). This effect can be achieved by suppressing cyclooxygenase 2 and inducing 15-OH-PG-dehydrogenase (28). Anastasi et al. have detected that there was a significant correlation between insufficient vitamin D levels and moderate to severe pelvic pain (29). On the other hand, in our study, the mean serum 25-OH-D levels in women with and without dysmenorrhea were not significantly different from each other in the endometriosis and non-endometriosis subgroups; serum 25-OH-D had no correlation with Dysmenorrhea-VAS scores.

In our study, the women who had bilateral endometrioma had significantly lower levels of vitamin D compared to the women with unilateral endometrioma. Moreover, Ciavattini et al. detected a significant linear correlation between 25-OH-D3 serum levels and the diameter of the ovarian endometrioma (30). However, Buggio et al. compared 217 women with endometriosis and 217 women without endometriosis and have shown that the serum vitamin D levels do not have any association with different phenotypes of endometriosis (26).

A possible hypothesis is the consumption of vitamin D by endometriosis or endometrioma. Vitamin D metabolism is very active in the reproductive tract. As the activity of the endometriotic tissue increases, it is also expected that the vitamin D metabolism or inactivation gains speed. Considering the anti-inflammatory role of vitamin D, which may act as a fire extinguisher and try to decrease the inflammatory process in endometriotic foci, it may be assumed that vitamin D is consumed by the endometriosis tissue. Ciavattini et al. detected a significant linear correlation between 25-OH-D3 serum levels and the diameter of the ovarian endometrioma (30). Since there is more endometriotic tissue in bilateral endometrioma than in unilateral endometrioma, it may be a possible explanation for the significant tendency to decline. In our study, the women with bilateral endometrioma had significantly lower levels of 25-OH-D compared to the women with unilateral endometrioma. Moreover, the endometrioma contains more endometriotic tissue compared to multiple small endometriosis foci scattered in the intraabdominal cavity. For that reason, the bilateral ovarian involvement, or in other words, the increased amount of endometriosis tissue, probably has a more important role in vitamin D metabolism than the presence of deep infiltrating endometriosis or Douglas obliteration. In our study, the serum 25-OH-D levels had no correlation with the presence of infertility, deep infiltrating endometriosis, or Douglas pouch obliteration; however, it had a significant negative correlation with the presence of bilateral endometrioma.

Considering the various factors such as form of vitamin D, vitamin D receptor status, gene polymorphism, and immunological status, which may influence the development of endometriosis as well as inconsistent results from the hitherto literature, it may be concluded that there is no single hypothesis to explain the effects of vitamin D on endometriosis. Moreover, it is not clear in the literature under which vitamin D threshold an immunological weakness would be observed.

In conclusion, the mean serum 25-OH-D levels were significantly decreased in both mild and moderate to severe endometriosis groups compared to the controls. There was no significant difference between the mild and moderate to severe endometriosis groups. The serum 25-OH-D levels had no correlation with the presence of infertility, deep infiltrating endometriosis, or Douglas pouch obliteration. The women who had bilateral endometrioma had significantly lower levels of 25-OH-D compared to the women with unilateral endometrioma. The mean serum 25-OH-D levels in women with and without dysmenorrhea were not significantly different from each other in the endometriosis and non-endometriosis subgroups. Serum 25-OH-D had no correlation with dysmenorrhea-VAS scores.

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