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Research Article / Araştırma

The relationship between ovarian endometrosis and vitamin D level

Ovaryan endometrozis ve D vitamini düzeyi arasındaki ilişki

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Anahtar Kelimeler: Endometriozis, D Vitamini, Anti-Müllerian Hormon, Parite, Sigara, İnfertilite.

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ABSTRACT

Introduction & Aim: The role of vitamin D in the pathogenesis of ovarian endometriosis is a subject that has been studied by researchers. This study was aimed to investigate the correlation between various features of ovarian endometriosis and vitamin D levels. **Material Methods:** Age, parity and smoking variables of the participants were examined as socio-demographic characteristics. Other variables examined in our study are endometrial stage, anti-Müllerian hormone and vitamin D levels, the side where endometriosis is seen, either right or left, the extent of endometriosis and infertility status. **Results**: According to the correlation analysis, there is a statistically significant, moderate relationship between vitamin D levels. According to the regression model, vitamin D in the blood has a negative and significant effect on the endometrial stage. According to these findings, it can be said that the decrease in vitamin D level will increase the endometrial stage status of the patient. **Conclusions**: The correlation between vitamin D and endometriosis, which is the primary subject of the research, was investigated with three different statistical methods.

ÖZ

Giriş ve Amaç: D vitamininin endometriozis patogenezindeki potansiyel rolü araştırmacılar tarafından üzerinde çalışılan bir konudur. Bu çalışma, overian endometriozisin çeşitli özellikleri ile D vitamini düzeyleri arasındaki ilişkiyi araştırmak amacıyla yapılmıştır. **Gereç Yöntemler:** Katılımcıların sosyodemografik özellikleri olarak yaş, parite ve sigara içme değişkenleri incelendi. Çalışmamızda incelenen diğer değişkenler evre, anti-Müllerian hormon ve D vitamini düzeyleri, endometriozisin, sağda veya solda, görüldüğü taraf, endometriozisin yaygınlığı ve infertilite durumudur. Tanımlayıcı istatistik, korelasyon, regresyon ve tek yönlü varyans analizi, t testi kullanılmıştır. **Bulgular**: Korelasyon analizine göre kandaki D vitamini düzeyi ile evre arasında istatistiksel olarak anlamlı, orta düzeyde bir ilişki vardır. Regresyon modeline göre kandaki D vitamininin evre üzerinde olumsuz ve anlamlı bir etkisi vardır. Bu bulgulara göre D vitamini seviyesindeki düşüşün hastanın evre durumunu yükselteceği söylenebilir. **Sonuç**: Araştırmanın birincil konusu olan D vitamini ile endometriozis arasındaki ilişki üç farklı istatistiksel yöntemle araştırıldı.

INTRODUCTION

Endometriosis is the placement of endometrial tissue outside the uterine cavity. It is characterized by the appearance of endometrium-like tissue outside the uterus. It is frequently seen in the reproductive age and progresses with the complaints of infertility and chronic pelvic pain. It is an estrogen-dependent, painful and chronic inflammatory disease. It can be a cause of infertility. In the retrograde theory, it is suggested that endometrial tissues are implanted in the peritoneal cavity or ovary during menstruation. It is stated in the metaplasia theory that endometriosis may have a malignant potential (1).

Although various theories have been proposed for the pathogenesis, the factors potentially playing a role in its etiology and progression have not been fully determined until now. It is accepted multifactorial. That includes hormonal, genetic, immunologic and parameters. Abnormal cytokine levels are detected in the peritoneal fluids and serum of patients. This suggests that inflammatory processes are important (2).

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Many effects have been shown in studies. Some autoimmune diseases and cancers are among the pathologies in which vitamin D has therapeutic effects. Low vitamin D levels are considered predisposing for autoimmune diseases such as diabetes mellitus, breast cancer, recurrent miscarriages, preeclampsia and rheumatoid arthritis. Receptor of vitamin D is expressed in epithelial cells of female reproductive system. Endometrial tissue expresses the enzyme 1α-hydroxylase, which is responsible for the conversion of 25-hydroxyvitamin D to calcitriol. Elocalcitol, a vitamin D receptor agonist, prevented the development of endometriosis in an endometriosis model. It has been reported that elocalcitol positively affects the implantation and organization of endometrial tissue. Vitamin D can induce apoptosis in endometriosis. Numerous research have found that deficiency of this vitamin increases the frequency of these diseases in endometriosis (3–5).

There is no a solid vote on the effects of vitamin D levels in endometriosis. There are some studies showing that the levels change in endometriosis. A prospective cohort study was conducted on participants who were laparoscopically confirmed to have endometriosis. The data obtained from the study indicated a correlation between increasing vitamin D levels and decreasing endometriosis. It has been reported that the risk of endometriosis is reduced by a quarter in the slice with the highest level of vitamin D. On the contrary, there are also studies in which women with endometriosis have high vitamin D levels (6,7).

This study was made clear to investigate the levels of vitamin D in patients presenting with ovarian endometriosis and the correlation between various features of ovarian endometriosis and levels of vitamin D.

MATERIALS AND METHODS

The women who applied to the Gynecology and Obstetrics Clinic of our hospital in the 10-year period between January 2011 and December 2020 constitute the sample of our retrospective study.

Inclusion criteria for the study:

- Range of 20-45 years,
- Detection of endometriosis,
- Detection of level of serum 25 OH vitamin D.

Exclusion criteria from the study:

- Perimenopausal and postmenopausal endometriosis patients
- No detection of level of serum 25 OH vitamin D.

150 endometriosis patients meeting the criteria above were included to the study . Information of the endometriosis patients included was obtained from patient records. Patients with missing records were excluded, and finally the study was continued with 101 participants . The research lasted three months.

In our study, age, parity and smoking variables of the participants were examined as socio-demographic characteristics. Other variables examined in our study are endometrial stage, anti-Müllerian hormone (AMH) level, vitamin D level, the side where endometriosis is seen, either right or left, the extent of endometriosis and infertility status. Analyzes were made regarding these variables, and their proportional and numerical distributions were given.

Based on the references :

- Below 20 ng/ml (50 nmol/L) - deficient
- Between 20 and 30 ng/ml (50-75 nmol/L) - insufficient,
- Below 30 ng/ml (75 nmol/L). nmol/L) was considered normal 8.

Based on the references :

- AMH value above 4 ng/ml is high,
- AMH value between 1.5 and 4 ng/ml is normal,
- AMH value between 0.5 and 1.5 ng/ml is low,
- AMH value belove 0.5 ng/ml is accepted as very low (9).

There are different scales of endometriosis. The most widely used scale is published by the American Society for Reproductive Medicine. The endometrial stage is determined by calculating the spread of the endometrial tissue, its depth and the affected areas of the body. According to this:

- Endometrial stage 1 or minimal: Scar tissue is so minimal that it is almost nonexistent.
- Endometrial stage 2 or mild: The implant is deeper.
- Endometrial stage 3 or medium: Many deep implants.
- Endometrial stage 4 or severe: There are many deep implants and thick adhesions (10).

Studies have shown that endometriomas with a diameter of ≤3 cm do not have a harmful effect on ovarian reserve. Therefore, in our study, endometriomas were divided into two groups as ≤3 cm and >3 cm, considering their size (11).

In our study, the ages of the participants were also examined by dividing them into groups. Participants in

our study are between the ages of 20-45. It is reported in the sources that the lowest period of labor complications is between the ages of 24-35. Based on this, the participants were included in the analysis by grouping them as <24 years, 24-35 years, and >35 years (12).

The side where endometriosis is seen, the extent of endometriosis, infertility, smoking and parity information were obtained from the files of the participants. These variables are considered to be predisposing factors to endometriosis.

Seasonal changes were taken into account when determining the vitamin D levels of the participants.

Ethical and administrative permissions for the study were obtained from the relevant committees of our institution (ATADEK 2021/02). Participation was carried out on a voluntary basis.

In the analysis of the data, descriptive statistics, correlation, regression and one-way analysis of variance, t-test were used. Post Hoc test was used to find out where the difference originates for the expressions that differ according to the results of the one-way analysis of variance. The confidence interval of the data is 95% (p=0.05).

RESULTS

In the model we created, endometrial stage was used as the dependent variable and the level of vitamin D was used as the independent variable. The fact that relationship between vitamin D and endometriosis was analyzed with advanced statistical methods in our study increases the reliability of the findings of our study.

In our study, the relationship between vitamin D and endometrial stages was examined with One Way Anova analysis in addition to correlation and regression analyses. A difference significant statistically was found between the variables. Vitamin D deficiency group has a higher endometrial stage level than other groups. This supports the findings of correlation and regression analyses.

1. Socio-demographic and other characteristics

The distribution of the participants according to their socio-demographic characteristics is shown in Table 1.

2. Vitamin D and Endometrial stage

Correlation analysis was performed to examine the relationship between participants' vitamin D levels and endometrial stage (Table 2). According to the results of the correlation analysis, there is a statistically significant, moderate relationship between vitamin D level in the blood and the endometrial stage (r=-0.583; p<0.01).

Table 1. Socio-Demographical and Other Characteristics of the Participants

	Frequency	Percentage
Size (Right)		
≤3 cm	58	57.5
>3 cm	43	42.5
Size (Left)		
<3 cm	59	58.4
>3 cm	42	41.6
Endometrial stage		
Low	20	19.8
Medium	6	5.9
High	44	43.6
Very high	31	30.7
Smoking Status		
Negative	92	91.1
Positive	9	8.9
Sekonder Infertility		
Negative	62	61.4
Positive	39	38.6

After the correlation analysis in the study, regression analysis was performed to measure the effect of vitamin D in the blood on the endometrial stage. The model created is statistically significant (F= 51.061; p=0.000). In the model, endometrial stage was used as the dependent variable and the level of vitamin D was used as the independent variable. According to the model, vitamin D (β= -0.583) has a negative and significant effect on the endometrial stage (t=20.338, p<0.001). Vitamin D explains 34% of the total variance. According to these findings, it can be said that the decrease in vitamin D level will increase the endometrial stage status of the patient (Table 3).

3. Examining the Correlations of Some Characteristics of the Participants with Other Variables

One Way Anova was used to examine whether there was a difference between other variables according to the age of the participants. The Post Hoc test was conducted to determine which age groups caused this difference. Accordingly, the difference for parity is due to the difference between the age group 36 years and over (2,250±1,014) and the other age groups. It was determined that the age group of 36 years and over had a higher mean than the other age groups (Table 4).

Accordingly, this difference is due to the difference between the 36 years and over (3.500±0.762) group and the other age groups. It was determined that the age group of 36 years and older had a lower mean than the other age groups (Table 4).

The statistically significant difference for infertility was due to the difference between the age group 36 years and over (1.227 ± 0.424) and the other age groups. It

Table 2. The Relationship Between Vitamin D Status and Endometrial stage in the Blood*

	Vitamin D Level	Endometrial stage
Vitamin D Level	1	**-.583****
Endometrial stage	**-.583****	1

**. Correlation is significant at the 0.01 level (2-tailed).
*Spearman Correlation

Table 3. The Effect of Vitamin D Status in the Blood on Endometrial stage*

Dependent variable	Independent variable	Non-Standardized Coefficients		Standardized Coefficients	t	p	R	R^2	F	p
		B	Std.Error	β						
Endometrial stage	**Constant**	4,183	0.206		20.34	0.000	0.583	0.34	51.061	0.000
	Vitamin D Level in the Blood	-0.968	0.135	-0.583	-7.146	0.000				

Table 4. Difference Analysis by Age *

	Age Group	n	Mean	Standard Deviation	F	p	Post Hoc
Parity	24 and under	9	1.000	0.000	18.116	**0.000**	3>1 3>2
	Between 25-35	48	1.375	0.606			
	36 and over	44	2.250	1.014			
AMH	24 and under	9	2.556	0.726	20.206	**0.000**	3>1 3>2
	Between 25-35	48	3.500	0.799			
	36 and over	44	2.500	0.762			
Vitamin D in the blood	24 and under	9	1.444	0.882	0.782	0.460	-
	Between 25-35	48	1.292	0.544			
	36 and over	44	1.455	0.697			
The size of endometriosis	24 and under	9	2.556	3.358	1.022	0.364	-
	Between 25-35	48	3.958	4.207			
	36 and over	44	2.886	3.901			
Endometrial stage	24 and under	9	2.889	0.782	0.353	0.703	-
	Between 25-35	48	2.938	1.060			
	36 and over	44	2.750	1.144			
Infertility	24 and under	9	1.667	0.500	5.043	**0.008**	3>1 3>2
	Between 25-35	48	1.479	0.505			
	36 and over	44	1.227	0.424			

1=age 24 and under; **2**= ages between 25-35; **3**= age 36 and over
* One-Way Anova

was determined that the age group of 36 years and over had a higher mean than the other age groups (Table 4).

Post Hoc test was performed to determine from which groups the difference originated. The difference, for parity, is due to the difference between the vitamin D deficiency (1.542±0.786) group and the vitamin D insufficiency (2.150±1.089) group. Vitamin D deficiency group has a lower mean than the other groups (Table 5).

The existence of the difference between vitamin D levels and the size of endometriosis was examined by one-way analysis of variance. A difference significant statistically was found between the variables ($p<0.05$) (Table 5).

A difference significant statistically was found between vitamin D levels and the endometrial stage of endometriosis ($p<0.05$). There was a difference between the vitamin D deficiency (3.250±0.746) group and the other groups. This is the basis of the significant difference. It was determined that the vitamin D deficiency group had a higher mean than the other groups (Table 5).

The possible differences between the participants and other variables according to their smoking status were analyzed with the t-test in independent samples. A difference significant statistically was found ($p<0.05$). According to this result, it was found that non-smokers had a higher mean for parity and AMH than non-smokers (Table 6).

For the dimension of endometriosis, it was found that those without infertility (2,565±3,932) had a lower mean than those with (4.641±3,849). In terms of endometrial stage, it was determined that those without infertility (2.548±1.082) had a lower mean than those with (3.333±0.869) infertility (Table 7).

DISCUSSION

A study have been conducted on the subject. In one of these studies, serum vitamin D levels were examined in over endometriosis. A possible relationship between the size of over endometriomas and serum levels of vitamin D has been investigated. In a cohort study, vitamin D deficiency was diagnosed in 42 (85.7%) of the participants. The proportion of ovarian endometriosis and D hypovitaminosis was relatively high. While the mean diameter was 40.2 ± 22.6 mm in participants with deficient ovarian endometrioma, it was 26.7 ± 12.1 mm in participants with normal vitamin D levels. Linear correlation was found between serum vitamin D levels and the diameter of ovarian endometriomas (13).

Another study aimed to determine vitamin D levels in endometriosis patients and to clarify the correlation between endometriosis and dietary calcium and vitamin D intake. 200 women with endometriosis and 154 healthy women as controls were included. The data obtained showed the correlation between vitamin D deficiency and the risk of endometriosis. It has also been determined that there is a correlation between dietary calcium deficiency and endometriosis recurrence. No similar correlation was observed between vitamin D intake and recurrence. It was concluded that vitamin D deficiency can be considered as a predisposing factor for endometriosis, and it was interpreted that high-dose calcium intake may be beneficial (14).

A meta-analysis study was conducted in which studies examining vitamin D levels in endometriosis were examined in some databases. Nine articles on the subject were included in the study. The results showed that women with endometriosis had lower levels of vitamin D than controls. A negative correlation was found between vitamin D level and the development of endometriosis. Although there is no difference statistically, the correlation between vitamin D deficiency and endometriosis has been demonstrated (15).

In addition to the studies listed above emphasizing the correlation between vitamin D deficiency and the development of endometriosis, there are also studies claiming the opposite. One of these studies was planned as a meta-analysis study. The PubMed database was searched. It was concluded that the data analyzed were not sufficient to prove a cause-effect relationship between vitamin D level and endometriosis (7).

Correlation and regression analyses were used in our research. The mathematical analysis of the correlation between two or more variables is examined by "Regression Analysis" and the direction and degree of the said relationship is examined by "Correlation Analysis". The result obtained from the correlation analysis does not necessarily imply a cause-effect relationship. "Regression Analysis" is used to investigate the relationship of cause-effect, and a model is created by determining the dependent and independent variables (16).

The relationship between endometriosis disease and AMH levels has been shown in some studies. In one of these studies, analyses of AMH levels and over reserve were performed in endometriosis patients. AMH levels were significantly lower in endometriosis. When the analysis was repeated by dividing the research cohort into two different age groups, it was shown that AMH levels could only explain the difference in women older than 36 (17).

These results are in full agreement with those obtained in our study. In our study, a difference was found between age groups and AMH levels statistically. According to the results of the analysis, it was determined that this

Table 5. Difference Analysis by Vitamin D Level *

	Vitamin D Level	n	Mean	Std.Dev.	F	p	Post Hoc
Parity	Deficiency	72	1.542	0.786	5.325	**0.006**	1<2
	Insufficiency	20	2.150	1.089			
	Adequate level	9	2.222	1.093			
AMH	Deficiency	72	3.028	0.839	1.361	0.261	-
	Insufficiency	20	2.650	1.040			
	Adequate level	9	2.889	1.167			
The size of endometriosis	Deficiency	72	3.542	2.858	10.582	**0.000**	1>2 1>3
	Insufficiency	20	1.450	2.282			
	Adequate level	9	0.000	0.000			
Endometrial stage	Deficiency	72	3.250	0.746	27.284	**0.000**	1>2 1>3
	Insufficiency	20	2.000	1.214			
	Adequate level	9	1.556	0.882			
Infertility	Deficiency	72	1.431	0.499	1.114	0.332	-
	Insufficiency	20	1.300	0.470			
	Adequate level	9	1.222	0.441			

1=Lower than 20 ng/mL (Vit. D deficiency); **2**= 21-29 ng/mL (Vit. D insufficiency); **3**= Higher than 30 ng/mL (sufficient level)

Table 6. Difference Analysis by Smoking Status*

	Smoking status	n	Mean	Standard Deviation	t	P
Parity	Not smoking	92	1.772	0.939	3.112	**0.007**
	Smoking	9	1.222	0.441		
AMH	Not smoking	92	3.000	0.877	2.123	**0.036**
	Smoking	9	2.333	1.118		
Vitamin D in the blood	Not smoking	92	1.370	0.641	-0.331	0.742
	Smoking	9	1.444	0.726		
The size of endometriosis	Not smoking	92	3.076	3.745	-1.724	0.120
	Smoking	9	6.333	5.545		
Endometrial stage	Not smoking	92	2.804	1.072	-1.421	0.158
	Smoking	9	3.333	1.000		
Infertility	Not smoking	92	1.370	0.485	-1.089	0.279
	Smoking	9	1.556	0.527		

Table 7. Difference Analysis by Infertility Status *

	Infertility	n	Mean	Standard Deviation	t	P
Parity	No	62	2.097	0.970	7.195	**0.000**
	Yes	39	1.128	0.339		
AMH	No	62	3.016	0.967	1.047	0.298
	Yes	39	2.821	0.823		
Vitamin D in the blood	No	62	1.452	0.694	1.569	0.120
	Yes	39	1.256	0.549		
The size of endometriosis	No	62	2.726	3.020	-0.389	0.698
	Yes	39	2.949	2.655		
Endometrial stage	No	62	2.548	1.082	-4.016	**0.000**
	Yes	39	3.333	0869		

*One-Way Anova

difference was caused by the difference between the age group of 36 and over and other age groups. It has been determined that the age group of 36 years and over has a lower average compared to other age groups.

Smoking is known to be a risk factor. Accordingly, it was determined that the AMH levels of the smokers were lower than the non-smokers, and the endometrial stages were higher. However, while the results of AMH levels are statistically significant, the results of the endometrial stage are not.

There is general agreement that endometriosis is more prone to be left-sided. In our study, right and left involvement were very close to each other. There was no statistical difference between them (18).

Studies have shown that endometriomas with a diameter of ≤3 cm do not have a harmful effect on ovarian reserve (19) (REFERENCES). This issue was also examined in our research. The data obtained indicate that the size of endometriosis decreases with the increase in vitamin D levels. This finding is also statistically significant.

CONCLUSION

According to the correlation analysis performed to examine the correlation between vitamin D and endometrial stage, a significant correlation between vitamin D level and endometrial stage was determined. As a result of the regression analysis, a statistically significant and negative correlation was found between vitamin D level and endometrial stage. Accordingly, it can be said that the decrease in vitamin D will increase the endometrial stage status of the patient.

Our research has some strengths. The sample size is good. It is possible to correctly calculate the possible correlations between the number of participants and the researched topics. The correlation, which is the primary subject of the research, was investigated with three different statistical methods. This is important for the reliability of our data.

The limitation of our study is that we cannot be sure of the reliability of the data we used, since it was designed retrospectively. Although the data that were thought to be unreliable were excluded from the analysis, it was considered that it would be beneficial to plan prospective studies with the same method.

Declaration of Competing Interest

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