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Vitamin D evaluation in adenomyosis: A retrospective cross-sectional study

Adenomyoziste D vitamini değerlendirmesi: Retrospektif kesitsel çalışma

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Abstract

Objective: Adenomyosis is a chronic inflammatory illness that depends on estrogen. In addition to its immune regulatory effects in chronic diseases, vitamin D also plays roles in regulating normal cell growth. In the present study, the purpose was to evaluate the possible relationships between serum 25-OH vitamin D levels and clinical and laboratory parameters in patients who were histopathologically diagnosed with adenomyosis.

Materials and Methods: A total of 168 females with a history of hysterectomy between January 2019 and November 2022 who were histopathologically diagnosed with adenomyosis and 168 women who were not diagnosed with adenomyosis were retrospectively evaluated in the present study. Demographic, clinical, and laboratory data were recorded at the time of admission. Visual analogue scale (VAS) scores were calculated for each patient to evaluate the severity of dysmenorrhea.

Results: There was a significant difference between the groups in terms of VAS: the adenomyosis group scored an average of 6, whereas the control group scored an average of 3 ($p<0.001$). The average platelet volume value of the patients was 8.6 fL in the adenomyosis group, and that of the control group was 7.2 fL, and it was detected to be significantly elevated in the adenomyosis group ($p<0.001$). The CA-125 value of the patients was 63.5 U/mL in the adenomyosis group, and that of the control group was 15.6 U/mL and it was detected to be significantly rised in the adenomyosis group ($p<0.001$). The 25-OH vitamin D level of the patients was 12.6 ng/mL in the adenomyosis group and that of the control group was 19.1 ng/mL and it was detected to be significantly elevated in the control group.

Conclusion: The current investigation provides compelling evidence for the association between low vitamin D levels and adenomyosis, which agrees with other research in the field. The current study's findings agree with other research that suggests vitamin D regulates cellular and signaling networks, including those that control cytokines and gene expression during adenomyosis. However, further studies are needed because data assassing the therapeutic efficacy of vitamin D in adenomyosis are questionable.

Keywords: Adenomyosis, dysmenorrhea, hysterectomy, 25-OH vitamin D

Öz

Amaç: Adenomyozis, östrojen bağımlı kronik enflamatuvar bir durumdur. D vitamini, kronik hastalıklardaki immün düzenleyici etkilerinin yanı sıra normal hücre büyümesinin düzenlenmesinde de rol oynar. Çalışmamızda histopatolojik olarak adenomyozis tanısı koyulan hastaların serum 25-OH vitamin D düzeyleri ile klinik ve laboratuvar parametreler arasındaki olası ilişkileri değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Çalışmamızda Ocak 2019-Kasım 2022 tarihleri arasında histerektomi yapılan ve histopatolojik olarak adenomyozis tanısı konulan 168 kadın ile adenomyozis tanısı konulmayan 168 kadın retrospektif olarak değerlendirildi. Başvuru sırasında demografik, klinik ve laboratuvar verileri kaydedildi. Dismenorenin şiddetini değerlendirmek için her hastada vizüel analog skala (VAS) puanı hesaplandı.

PRECIS: Our study strongly supports the association between low 25-OH D vitamin levels and adenomyosis and deep infiltrative endometriosis.

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Bulgular: Adenomyozis grubunda VAS ortalaması 6, kontrol grubu vizüel ağrı skoru ortalaması ise 3 saptanmış olup gruplar arasında anlamlı fark saptanmıştır (p<0,001). Adenomyozis grubunda hastaların ortalama trombosit hacim değeri 8,6 fL, kontrol grubundakilerin ise 7,2 fL saptanmış olup, adenomyozis grubunda anlamlı yüksek saptanmıştır (p<0,001). Adenomyozis grubunda hastaların CA-125 değeri 63,5 U/mL, kontrol grubundakilerin ise 15,6 U/mL saptanmış olup, adenomyozis grubunda anlamlı yüksek saptanmıştır (p<0,001). Adenomyozis grubunda hastaların 25-OH D vitamini seviyesi 12,6 ng/mL, kontrol grubundakilerin ise 19,1 ng/mL saptanmış olup, kontrol grubunda anlamlı yüksek saptanmıştır.

Sonuç: Literatürdeki çalışmalar ile uyumlu olarak, çalışmamız düşük D vitamini düzeyleri ile adenomyozis arasındaki ilişkiyi güçlü bir şekilde desteklemektedir. Çalışmamız, adenomyozisde gen ekspresyonları ve sitokinleri içeren, hücresel ve sinyal yollarının düzenlenmesinde D vitamininin rolünü öne süren çalışmalarla tutarlı olmuştur. Bununla birlikte D vitamininin adenomyozisdeki terapötik etkinliğini değerlendiren veriler şüpheli olduğundan ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Adenomyozis, dismenore, histerektomi, 25-OH D vitamini

Introduction

The development of endometrial glands and stroma in in the myometrium is a characteristic of the estrogen-dependent chronic inflammatory disease known as adenomyosis. Following reactive hypertrophic and/or hyperplastic changes to the surrounding myometrium, adenomyosis results in uterine enlargement[1]. The presence of endometrial tissue along the inner surface of the uterus outside the uterus is a characteristic of chronic endometriosis. The endometrial origin and the anatomical location of the lesions are thought to be the two main distinctions between endometriosis and adenomyosis[2]. Endometriosis and adenomyosis share several characteristics in terms of symptomatology, histology, and molecular changes[3,4]. There are distinctions in the pathogenesis and pathogenic mediators of these two separate diseases[5]. Invagination of the basalis endometrium into the myometrium and *de novo* development from metaplasia of embryonic mullerian remnants or endometrial stem/progenitor cells with the myometrium are the two most widely recognized ideas about the pathophysiology of adenomyosis. Previous investigations have identified a panel of pathways involving tissue damage or injury at the endometrial-myometrial interface, which can result in inflammation, localized production of estrogen, and the adenomyosis development[6]. Adenomyosis often develops in the 4th-5th week of life during the middle of a decade and after childbearing is finished. Nevertheless, newer imaging techniques, including magnetic resonance imaging and transvaginal ultrasonography, have revealed that adenomyosis can also affect younger females[7]. Adenomyosis patients have various issues, including severe painful symptoms and reduced quality of life due to irregular uterine bleeding. This progressive illness can lead to infertility or subfertility that requires appropriate treatment[8]. Although it is common and the symptoms are severe, little data are available about its pathogenesis. The reason for this may be because of the long-standing dependence on histopathological examination of uterine samples after hysterectomy and the lack of reliable preoperative diagnosis for disease diagnosis[9]. Because of variations in the diagnostic criteria and methods for obtaining myometrial samples, histological evaluation of hysterectomy tissues reveals a prevalence of adenomyosis ranging from 5% to 70%[10]. It has been reported that many risk factors such as alcohol use, smoking, body mass index (BMI), age at menarche, and parity may be responsible for the pathogenesis of adenomyosis[11]. In addition to these risk factors, other risk factors that are still controversial are included in the literature. One of these factors, vitamin D, plays a role in regulating both healthy cell development and immune system effects in chronic diseases[12]. vitamin D stimulates the synthesis of anti-inflammatory cytokines while decreasing the production of pro-inflammatory cytokines, in addition induce programed cell death, and suppresses neovascularization[12]. Considering these data, our purpose was to assess potential relationships between serum 25-OH vitamin D levels and laboratory and clinical characteristics in individuals with histopathologically confirmed adenomyosis diagnoses.

Materials and Methods

This study was designed in a retrospective cross-sectional fashion following the Helsinki Declaration. An informed consent form was received from the patients, and the rules regarding animal rights were followed. The study received approval from the Ethics Committee of Dokuz Eylül University School of Medicine (date: 13/09/2023, number: 2023/28-20). A total of 168 women who underwent hysterectomy and were histopathologically diagnosed with adenomyosis between January 2019 and November 2022 and 168 women who were not diagnosed with adenomyosis were retrospectively evaluated. The study group contained both premenopausal and postmenopausal females between the ages of 35 and 50 years with histopathologically detected adenomyosis. The control group contained 168 females who underwent hysterectomy because of abnormal uterine bleeding, postmenopausal bleeding, myoma uteri, and adnexal mass, and no adenomyosis was detected. Patients with vitamin D use during the last 6 months before operation, the presence of any systemic disease, the presence of known malignancy, menopause and hormone replacement therapy, oral contraceptive use, and a known diagnosis of bilateral or unilateral endometrioma were excluded from the study. Laboratory, clinical, and demographic data (e.g., age, BMI, smoking, age at first menarche, alcohol consumption, and obstetric history) were recorded at the time of admission. Visual analogue scale (VAS) scores were calculated for each patient to evaluate the severity of dysmenorrhea. A VAS value of "0" denoted the absence of pain, whereas a VAS value of "10" represented the maximum level of discomfort. The presence of

deep infiltrative endometriosis (DIE) detected during surgery was retrospectively obtained from patient files.

Statistical Analysis

The analyses were conducted using SPSSx26.0 (IBM Inc., Chicago, IL, USA). Normality analysis was conducted using the Kolmogorov-Smirnov test. The quantitative data of the patients were reported as mean ± standard deviation (minimum-maximum). Non-normally distributed variables were analyzed using the Mann-Whitney U test. These outcomes are presented as median (minimum-maximum) values for each group. Fisher's Exact test and the chi-square test were employed to assess the categorical data, and the results are presented as counts and percentages (%). A 95% confidence interval was used to analyze the results. A p-value less than 0.05 was regarded as statistically significant.

Results

In this research, the average age of the participants was 43±3.9, and no significant difference was detected between the adenomyosis groups and the control group (p=0.1). The average BMI of the participants was 22.6±1.5 kg/m^2, age at menarche was determined as 12±1, and no significant difference was detected between the groups in this respect (p=0.9, p=0.3, respectively). The average gravida of the participants in this research was 2.2±0.9, the parity mean 2±0.8, and no significant difference was observed between the groups (p=0.5, p=0.07, respectively). No significant difference was observed between the groups with regard to smoking and alcohol use of the patients (p=1, p=0.8, respectively). The average visual pain score in the adenomyosis group was 6, and the average visual pain score in the control group was 3. A significant difference was detected between the groups in this respect (p<0.001). No significant difference was detected about operation indications between the patients in the adenomyosis group and the control group (p=0.8). The presence of DIE was detected to be significantly elevated in the adenomyosis group than in the control group (p<0.001) (Table 1).

The average hemoglobin of the participants in the adenomyosis group was 11.1 g/dL, and that of the control group was 11.3 g/dL, and it was detected to be significantly elevated in the control group (p<0.001). The average hematocrit of the patients was 33.5% in the adenomyosis group and 34.1% in the control group, and it was detected to be significantly elevated in the control group (p<0.001). The average leukocyte level of the patients was detected to be 7.5±1.2 n/mL, and no significant difference was detected between the groups (p=0.09). The average platelet volume value of the patients in the adenomyosis group was 8.6 fL, and that of the control group was 7.2 fL, and it was detected to be significantly elevated in the adenomyosis group (p<0.001). The neutrophil/lymphocyte ratio (NLR) of the patients in the present study was 1.8±0.5, the platelet/lymphocyte ratio (PLR) was 98.8±34.5, and no significant difference was detected between the groups in this respect (p=0.7, p=0.6, respectively). The CA-125 value of the patients was 63.5 U/mL in the adenomyosis group, and that of the control group was 15.6 U/mL, and it was detected to be significantly increased in the adenomyosis group (p<0.001). The 25-OH vitamin D level of the patients in the adenomyosis

Table 1. Demographic and clinical characteristics of the groups

Variables	Group 1 (n=168, 50%)	Group 2 (n=168, 50%)	All patients (n=336, 100%)	p-value
Age (years)	43 (35-50)	44 (35-52)	43±3.9 (35-52)	0.1
BMI (kg/m^2)	22.6 (18.7-29.4)	22.6 (18.6-29.1)	22.6±1.5 (18.6-29.4)	0.9
Age at menarche (years)	12 (10-15)	12 (10-15)	12±1 (10-15)	0.3
Gravida	2 (0-6)	2 (0-4)	2.2±0.9 (0-6)	0.5
Parity	2 (0-5)	2 (0-4)	2±0.8 (0-5)	0.07
Smoking (10 packs/day)	28.6% (48/168)	28.6% (48/168)	28.6% (96/336)	1.0
Alcohol	29.8% (50/168)	28.6% (48/168)	29.2% (98/336)	0.8
VAS	6 (3-9)	3 (1-9)	4.8±1.8 (1-9)	<0.001
Operation indication				
*Abnormal uterine bleeding	32.1% (54/168)	27.4% (46/168)	29.8% (100/336)	0.8
*Postmenopausal bleeding	11.3% (19(168)	12.5% (21/168)	11.9% (40/336)	
*Myoma uteri	35.1% (59/168)	36.3% (61/168)	35.7% (120/336)	
*Adnexal mass	21.4% (36/168)	23.8% (40/168)	22.6% (76/336)	
Presence of deep infiltrative endometriosis	30.4% (51/168)	0% (0/168)	15.2% (51/336)	<0.001

BMI: Body mass index, VAS: Visual analog scale

group was 12.6 ng/mL, and that of the controligroup was 19.1 ng/mL, and it was detected to be significantly elevated in the control group (p<0.001) (Table 2).

The mean hemoglobin of the adenomyosis patients was 10.8±0.6 g/dL in the present study, and the average hematocrit was 32.8±2%, and no significant difference was detected between positive and negative patients for the presence of DIE (p=0.5, p=0.7, respectively). The mean leukocyte count of the adenomyosis patients was 7.6±1.1 n/mL, the mean platelet volume value was 8.6±0.5 fL, and no significant difference was observed between the groups (p=0.8, p=0.7, respectively). The NLR of the adenomyosis patients in this research was 1.7±0.5, the PLR was 96.2±29.4, and no significant difference was detected between the groups in this respect (p=0.8, p=0.5, respectively). The mean CA-125 of the adenomyosis patients was 66.2±20 U/mL, and no significant difference was detected between the groups (p=0.6). The 25-OH vitamin D level of patients with positive DIE presence was detected to be 12.3 ng/mL, and that of patients with negative DIE presence was 13.1 ng/mL, and it was detected to be significantly lower in the DIE positive group (p=0.03) (Table 3).

Discussion

The visual pain score was detected to be elevated in the adenomyosis group than in the control group in this study. The mean platelet volume level was elevated in the adenomyosis group compared with the control group. CA-125 level was elevated in the adenomyosis group compared with the control group. The average 25-OH vitamin D level in the DIE-positive group was lower than that in the DIE-negative group. The majority of studies conducted on vitamin D and adenomyosis in the literature suggest that increased dairy product consumption and omega-3 fatty acid consumption are linked to a lower incidence of endometriosis and adenomyosis by providing high levels of 1.25-OH vitamin D3 in the circulation[13-15]. Previous studies in the literature report that Vitamin D Binding Protein (VDBP) significantly increases ectopic endometrium and serum VDBP levels are elevated in females with endometriosis and adenomyosis[16,17].The pathophysiology of this association may include variation in VDBP (GC-2) levels, as proposed by Faserl et al.[17]. females with endometriosis are more likely to have the GC-2 polymorphism. The GC-2 polymorphism may be linked to insufficient macrophage phagocytism activation, perhaps leading to an inability to stop the implantation of endometriotic tissue in the peritoneum. Becker et al.[18] showed that 1α-hydroxylase expression in damaged endometrial tissue was significantly elevated compared with that in healthy tissues. However, there are conflicting reports in the literature regarding this relationship. Hartwell et al.[19] suggested that the serum 25-OH-D3 level increased in females with damaged endometrial tissue compared with the control group and that this difference was statistically significant. Delbandi et al.[20] reported that 25-OH-D3 levels were similar for females having and not having adenomyosis. However, these outcomes are not in line with the outcomes of other research suggesting that high dietary vitamin D intake decreases the risk of developing adenomyosis and endometriosis. A higher demand for vitamin D can be inferred from women with endometriosis who had elevated VDBP concentrations in both their blood and endometriotic tissue. Becker et al.[18] reported an increase in receptor synthesis and an acceleration of the conversion of vitamin D to its active form in endometriotic tissue. It was found in this study that serum 25-OH-D3 levels decreased in females with adenomyosis, in accordance with these findings. Skowrońska et al.[21] according to his suggestion, the severity of the sickness determines the level of vitamin D. This study demonstrated a correlation between DIE and 25-OH vitamin D levels. Therefore, our findings suggest that the 25-OH vitamin D level may be used as a marker to gauge the severity of the illness. According to Helde-Frankling and Björkhem-Bergman[22], vitamin D consumption is linked to a reduction in pain, which may be the consequence of prostaglandin (PG) inactivation and reduced production. 15

Table 2. Laboratory characteristics of the groups

Variables	Group 1 (n=168, 50%)	Group 2 (n=168, 50%)	All patients (n=336, 100%)	p-value
Hemoglobin (g/dL)	11.1 (8.1-12.2)	11.3 (8.6-12.3)	11±0.6 (8.1-12.3)	<0.001
Hematocrit (%)	33.5 (25.5-38.1)	34.1 (25.6-36.8)	33.3±1.8 (25.2-38.1)	<0.001
Leukocyte (n/mL)	7.6 (4.5-11.6)	7.5 (4.2-11.4)	7.5±1.2 (4.2-11.6)	0.09
MPV (fL)	8.6 (7.5-9.8)	8.2 (7.4-9.2)	8.4±0.5 (7.4-9.8)	<0.001
NLR	1.6 (0.9-3.9)	1.6 (0.9-3.8)	1.8±0.5 (0.9-3.9)	0.7
PLR	91.9 (39.3-194.5)	92.5 (41.4-233.3)	98.8±34.5 (39.2-233.3)	0.6
CA-125 (U/mL)	63.5 (19.8-152.6)	15.6 (8.6-54.1)	41.4±28.9 (8.6-152.6)	<0.001
25-OH vitamin D (ng/mL)	12.6 (8.9-31.2)	19.1 (10.8-34.5)	16.1±4.2 (8.9-34.5)	<0.001

NLR: Neutrophil/lymphocytei ratio, PLR: Platelet/lymphocytei ratio, MPV: Mean platelet volume

Table 3. Comparison of laboratory characteristics of adenomyosis cases according to the presence of deep infiltrative endometriosis (DIE)

Variables	Group 1 (DIE+) (n=51, 30.4%)	Group 2 (DIE-) (n=117, 69.6%)	All patients (n=168, 100%)	p-value
Hemoglobin (g/dL)	11.1 (8.1-12.1)	11.1 (8.8-12.2)	10.8±0.6 (8.1-12.2)	0.5
Hematocrit (%)	33.5 (25.5-36.2)	33.5 (25.6-38.1)	32.8±2 (25.5-38.1)	0.7
Leukocyte (mL)	7.8 (4.5-10.8)	7.6 (4.5-11.6)	7.6±1.1 (4.5-11.6)	0.8
MPV (fL)	8.6 (7.5-9.8)	8.6 (7.6-9.7)	8.6±0.5 (7.5-9.8)	0.7
NLR	1.6 (0.9-3.6)	1.6 (0.9-3.9)	1.7±0.5 (0.9-3.9)	0.8
PLR	94.9 (53.2-194.5)	90.7 (39.3-181.7)	96.2±29.4 (39.2-194.5)	0.5
CA-125 (U/mL)	68.4 (30.6-152.6)	61.5 (19.8-108.6)	66.2±20 (19.8-152.6)	0.06
25-OH-D vitamin (ng/mL)	12.3 (8.9-31.2)	13.1 (9.1-22.5)	13.1±2.5 (8.9-31.2)	0.03

NLR: Neutrophil/lymphocytei ratio, PLR: Platelet/lymphocytei ratio, MPV: Mean platelet volume

OH-PG dehydrogenase can be induced and cyclooxygenase 2 can be suppressed to accomplish this. Anastasi et al.[23] reported a significant relationship between insufficient 25-OH vitamin D levels and severe and moderate pelvic pain. Given that 25-OH vitamin D has anti-inflammatory properties and can reduce inflammation in endometriotic foci, it is possible that injured endometriotic tissues consume 25-OH vitamin D. A substantial linear association between blood 25-OH vitamin D levels and the width of ovarian endometrioma was observed by Ciavattini et al.[24]. This may be a possible explanation for the significant decreasing trend because there is more endometriotic tissue in bilateral endometrioma than in unilateral endometrioma. Considering the factors that may affect the development of adenomyosis, such as vitamin D form, receptor status of vitamin D, gene polymorphism, and immunological status, in addition to the inconsistent results in the literature, it can be concluded that several theories account for the effects of vitamin D on adenomyosis. Nevertheless, the precise vitamin D threshold level at which immune impairment occurs is unclear.

Study Limitations

The present study had some limitations, such as being retrospective, a limited number of patients, and the use of patient records in the healthcare system. This study sheds light on the previously unexplored link between 25-OH vitamin D and adenomyosis. It also had strengths, such as representing one of the few studies revealing the link between 25-OH vitamin D and dysmenorrhea.

Conclusion

The present study results are consistent with the data of other studies in the literature. This study strongly supports the link between low vitamin D levels and adenomyosis. This study is also consistent with studies reporting the role of vitamin D in regulating cellular and signaling pathways, including gene expression and cytokines, in adenomyosis. However, further studies are needed because there is doubtful evidence to assess the therapeutic effectiveness of vitamin D in adenomyosis. Further study is necessary because the evidence supporting the use of increasing dietary vitamin D consumption as a preventative strategy is limited, despite the encouraging statistics.

Ethics

Ethics Committee Approval: The study received approval from the Ethics Committee of Dokuz Eylül University School of Medicine (date: 13/09/2023, number: 2023/28-20).
Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: U.A., S.E., Concept: O.Y., Design: O.Y., Data Collection or Processing: H.A.A., C.A., T.B.B., Analysis or Interpretation: T.B.B., Literature Search: H.A.A., C.A., Writing: U.A, S.E.
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