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What is the effect of vitamin D deficiency on Pap smear test results in the postmenopausal period?

Asena AYAR MADENLİ[1,*], İnci ÖZ[2], Ergül DEMİRÇİVİ[3]

[1]Department of Obstetrics and Gynecology, İstinye University, Liv Hospital, İstanbul, Türkiye
[2]Department of Obstetrics and Gynecology, Kağıthane Kızılay Hospital, İstanbul, Türkiye
[3]Department of Obstetrics and Gynecology, Prof. Dr. Süleyman Yalçın City Hospital, İstanbul, Türkiye

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Abstract

This study aimed to determine the impact of vitamin D deficiency on Pap smear test results in women in the postmenopausal period. This cross-sectional study included 394 women who applied to İstanbul Medeniyet University, Göztepe Training and Research Hospital gynecology and obstetric clinic for routine Pap smear tests. This study was conducted between May 2019 and December 2020. Cases were divided into severe deficiency (<12 ng/ml), moderate deficiency (12-20 ng/ml), deficiency (21-30 ng/ml), and sufficiency (>30 ng/ml) according to the vitamin D levels measured in the postmenopausal period within the scope of check-up examinations. Pap smear test results compared with vitamin D levels. The mean age of the study group was 48.70±3.46 years. There was a statistically significant association between vitamin D values and Pap smear test results ($p<0.05$). Vitamin D greater than 20 ng/ml had a significant relationship with the normal cytology results. There was a statistically significant association between vitamin D lower than 20 ng/ml and cervicitis cytology results. The results showed that the serum vitamin D and the Pap smear test results had a significant association. It is recommended that physicians prescribe the use of vitamin D supplements in women in the high-risk group of cervical cancer.

Keywords: cervical cancer, vitamin D, Pap smear test, cervical cytology

1. Introduction

Several experts considered vitamin D a lipid-soluble hormone in steroid structure, causing different effects in different tissues (1, 2). Vitamin D has been extensively studied as a steroid in the extraskeletal system. In previous studies, vitamin D has been reported to affect several physiologic systems with various clinical influences, such as protection against degenerative disease and cancer prevention (2, 3). Since vitamin D is a naturally synthesized substance, it is an attractive material in cancer treatment and prevention studies (4). The relationship between vitamin D and the progression of cancer, known as the "Vitamin D/cancer hypothesis," has attracted the attention of researchers, particularly in the last two decades (5). The immune modulation of B and T lymphocytes is facilitated by vitamin D, playing an essential role in the natural immune system, proving them to differentiate in the adaptive immune system. This helps monocytes become macrophages and enhances their phagocytosis capacity (6).

Cervical cancer, the fourth most common cancer among women, is a global public health problem, of which the death rate is expected to reach 13.400.000 by 2070 (7, 8). Cervical cancer has quite a high incidence due to either nonexistent or poorly implemented prevention programs. Developing countries have the highest number of cases and deaths caused by cervical cancer (9). The reason is that cancer prevention and control programs are not sufficient in these countries. In developed countries, about 80% of cervical cancers have been reduced by implementing effective prevention programs and effective treatments in the early stages of cancer (10). Effective preventive health behavior in this field is to perform a Pap smear test. A Pap smear test is an easy screening method to evaluate infection and investigate the pre-cancer changes and cervical cancer (11, 12). It is an effective way to prevent cervical cancer development and a noninvasive, simple, easy, and cost-effective way to detect precancerous lesions (13). In communities with active screening programs, the death rate caused by this cancer has decreased by 40% in the past thirty years. Based on the studies, 44% of women are aware of cervical cancer screening programs and have refereed at least once for this test in Sweden (14).

Many studies have evaluated the identification of factors affecting Pap smear test results. The present study assessed the relationship between vitamin D and Pap smear results. It is essential to determine factors affecting the Pap smear test results to provide treatments to reduce costs and increase the success of the treatment. This study aims to evaluate the relationship between vitamin D and Pap smear results.

*Correspondence: asenaayar@yahoo.com.tr

2. Materials and Methods

The Ethics Committee of İstanbul Medeniyet University approved this prospective cross-sectional study. (Date: 13.01.2021 Decision no: 2021/0041). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. With the ethics committee's approval, the data were scanned retrospectively using the Hospital Information Management System.

We included patients who applied within the scope of the postmenopausal routine check-up program and had a Pap smear test and their vitamin D level checked. Three hundred ninety-four women participated in this study between May 2019 and December 2020.

All surgical pathology and Pap smear files were searched for "routine" Pap smears after the approval of the Institutional Review Board. We classified abnormal routine Pap smears into the following categories based on the latest Bethesda system: Atypical squamous cells of undetermined significance (ASC-US), atypical glandular cells of undetermined significance (AGUS), low-grade squamous intraepithelial lesion (LGSIL), high grade squamous intraepithelial lesion (HGSIL), and cervicitis. If available, we performed correlation with tissue biopsy from the cervix for each abnormal Pap smear. Serum vitamin D values were recorded from the hospital information management system. The scale for measuring hormones was Nanograms per milliliter (ng/ml). Patients were clustered as subjects severe deficiency (<12 ng/ml) (n=127), moderate deficiency (12-20 ng/ml) (n=70), insufficiency (21-30 ng/ml) (n=122), and sufficiency (>30ng/ml) (n=75) groups.

2.1. Statistical analysis

We used the Kolmogorov-Smirnov test to check the normality and measured Mean and standard deviations (SD) to check each continuous variable, including age, serum vitamin D, gravida, parity, abortus, body mass index (BMI), the coital debut age, and menopause.

We used the Chi-square and the Pairwise Z-Tests tests to study the difference between groups and SPSS v22 for statistical analyses. A value of $p < 0.05$ was accepted as statistically significant. To calculate the sample size with the G-Power 3.1 program, we measured two groups' total mean based on the Z test with the power of 75%, 0.5 proportion p1, 0.6 proportion p2, and 0.1 type 1 error for at least 378 women (15).

3. Results

Women's mean age and BMI were 48.70 ± 3.46 and 25.04±2.13, respectively. The frequency for the serum vitamin D<12 ng/ml interval is 127 (32.2%). The frequency for the vitamin D (12-20 ng/ml), vitamin D (21-30 ng/ml) and vitamin D (>30ng/ml) were 70 (17.8%), 122 (31%), and 75 (19%), respectively.

The mean vitamin D level was 20.05±11.82. The mean vitamin D level of four groups of women in the study, severe deficiency, moderate deficiency, insufficiency, and sufficiency were 7.09±1.50, 15.47±1.94, 25.13±2.09, and 37.98±7.18, respectively. Table 1 shows descriptive statistics of study parameters.

Table 1. Descriptive statistics of study parameters in women (n=394)

Study parameters	median (range) mean ± SD
Age (yr)	47 (41-58) 48.70±3.46
Vitamin D	20 (4.6-66) 20.05±11.82
Gravida	1 (0-2) 1.12±0.55
Parity	1 (0-1) 0.58±0.49
Abortus	0 (0-2) 0.52±0.62
BMI	25 (19-30) 25.04±2.13
The coital debut age (yr)	25 (18-31) 24.37±2.53
Menopause (yr)	3 (1-7) 3.27±1.84

SD, standard deviation.

Table 2 shows the frequency of Pap smear test results and the mean and SD of vitamin D values in each Pap test result. Women with normal Pap test results had the highest vitamin D levels (23.87±11.98). As stated in Table 2, the highest frequency of Pap smear results was normal 175 (44.4%), cervicitis 121 (30.7%), ASCUS 60 (15.2%), AGUS 9 (2.3%), LGSIL 21 (5.3%), and HGSIL 8 (2%).

Table 2. The frequency of Pap smear test results

Study parameters		n (%)	Vitamin D (mean ± SD)
Pap smear test results	Normal	175 (44.4)	23.87±11.98
	AGUS	9 (2.3)	18.98±10.45
	ASCUS	60 (15.2)	16.48±11.29
	LGSIL	21 (5.3)	17.14±10.4
	HGSIL	8 (2)	16.95±15.58
	Cervicitis	121 (30.7)	17.1±10.45

As stated in Table 3, a chi-square test found a statistically significant association between vitamin D levels and Pap smear test results ($p<0.001$). The Pairwise Z-Tests found that the percentage of women who had the normal cytology results was significantly higher for those who had vitamin D (21-30ng/ml and > 30ng/ml) than for those who had vitamin D lower than 20ng/ml.

Table 3. The relationship between Pap test results and vitamin D levels

Study parameters		<12 ng/ml n (%)	12-20 ng/ml n (%)	21-30 ng/ml n (%)	>30 ng/ml n (%)	*p*
Pap smear test results	Normal	32 (25.2)	26 (37.1)	**69 (56.6)†**	**48 (64.0)†**	<0.001*
	AGUS	3 (2.4)	2 (2.9)	3 (2.5)	1 (1.3)	
	ASCUS	30 (23.6)	8 (11.4)	14 (11.5)	8 (10.7)	
	LGSIL	9 (7.1)	5 (7.1)	4 (3.3)	3 (4.0)	
	HGSIL	4 (3.1)	2 (2.9)	1 (0.8)	1 (1.3)	
	Cervicitis	**49 (38.6)†**	**27 (38.6)†**	31 (25.4)	14 (18.7)	

*A Chi-square test. † Pairwise Z-Tests

Fig. 1 shows vitamin D levels in different Pap smear test results.

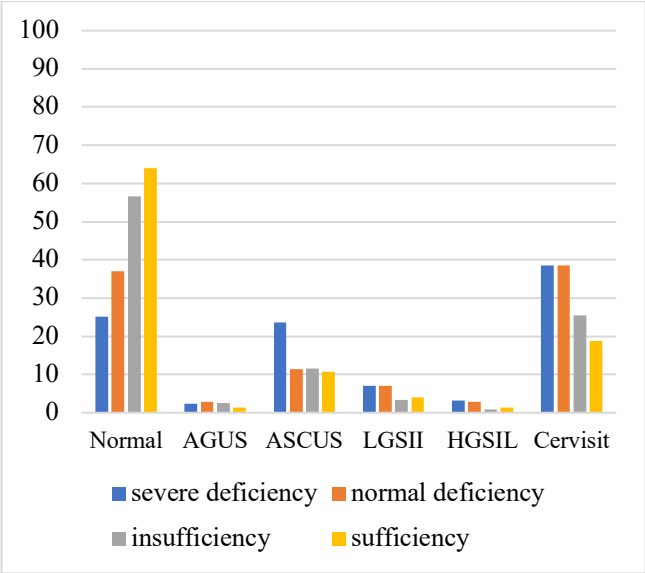

Fig. 1. Vitamin D levels in different Pap smear test results

4. Discussion

In the current study, we researched the association between Pap smear results and vitamin D levels in women. Of the 394 sexually active women, 175 (44.4%) had normal cytology results, and 219 (55.6%) women had abnormal cytology. The frequency of abnormal cytology was 2.3% (n=9) for AGUS, 15.2% (n=60) for ASCUS, 5.3% (n=21) for LGSIL, 2% (n=8) for HGSIL, and 30.7% (n=121) for cervicitis. There was a significant association between Vitamin D and Pap smear results. According to research findings, the value of vitamin D greater than 20 has a statistically significant relationship with normal cytology results. The value of vitamin D lower than 20 has a statistically significant relationship with cervicitis cytology results. By increasing vitamin D's value, the normal cytology results frequency has increased. Therefore, there is a statistically significant relationship between the normal cytology results and vitamin D.

Vitamin D, which has several vital functions, includes vitamins D1, D2, and D3 as a fat-soluble vitamin in a family of compounds. The most important functions of vitamin D for the body include: reducing the risk of multiple sclerosis (16), decreasing the chance of heart disease (17), decreasing the likelihood of severe illnesses (18), supporting weight loss (19), supporting immune health (20), and reducing the possibility of depression (21). The effect of vitamin D on women with polycystic ovary syndrome (PCOS) (22), osteoporosis in women (23), and pregnancy period was investigated in many studies (24). Our study showed that vitamin D positively affects Pap smear results. The value of 20ng/ml was an important criterion. More or less than this value will affect the Pap test results. Patients were clustered as insufficiency (21-30ng/ml) and sufficiency (>30ng/ml) groups were normal cytology results.

Sharif (25) reported that conservative sexual behavior, religious norms, and low smoking rates impact pap smear results. Sachan et al. (26) found in a study on the patients' demographic profile affecting results of pap smear tests that HGSIL and LGSIL were first seen in 41–50 year women, and a significant risk factor for cervical carcinoma is multiparity (>3). According to Gosh et al. (27), there is an association between the results of pap smear and younger age at sexual debut, a more youthful age group, and lower socioeconomic status. the positive association between the infections and young age is due to more sexual activity of younger women increasing their susceptibility to sexually transmitted infections. In several studies, socioeconomic status affecting Pap smear results was reported due to few health check-ups and poor hygiene (28-30). Studies found age and socioeconomic status to be critical factors in cervical cancer screening, affecting Pap smear test results.

The shortcoming of the study was that all samples were recovered from a single center whereas the high number of samples can be counted as its strength.

In conclusion, vitamin D may have some beneficial effects on the Pap smear test results in women. Therefore women in the high-risk group for cervical cancer may be advised to regularly check their vitamin D status. The heavy burden of cervical cancer to the health system warrants any medication which has clinically proven benefits. This study suggests that maintaining the normal levels of Vitamin D, which plays a supportive role in immune system may be an efficient yet cheap and easy accessible way to fight cervical precancerous lesions before they evolve into cervical cancer.

Ethical statement

The Ethics Committee of İstanbul Medeniyet University approved this prospective cross-sectional study. (Date: 13.01.2021 Decision no: 2021/0041).

Conflict of interest

The authors have no conflicts of interest to declare.

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None to declare.

Authors' contributions

Concept: A.A.M., İ.Ö., Ö.D., Design: A.A.M., İ.Ö., Ö.D., Data Collection or Processing: A.A.M., İ.Ö., Ö.D., Analysis or Interpretation: A.A.M., İ.Ö., Ö.D., Literature Search: M A.A.M., İ.Ö., Ö.D., Writing: A.A.M., İ.Ö., Ö.D.

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