






# The effect of vitamin D on the regression of human papilloma virus infection and metabolic parameters: a retrospective study

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**Purpose:** Human papillomavirus (HPV) is the primary cause of cervical cancer. Our study aims to evaluate the effects of vitamin D on HPV regression, related cytological pathologies and various metabolic parameters. **Materials and methods:** 100 high-risk HPV positive patients, who were detected from hospital database, were divided into 2 groups as those who received vitamin D supplements (n = 50) and did not receive vitamin D supplements (n = 50). We determined the changes in serum vitamin D concentrations, metabolic parameters of patients and regression of HPV after 6 months. Then, we compared the results of patients who took vitamin D supplements, and those who did not. **Results:** Patient characteristics of both groups were similar in terms of smoking, using oral contraceptives, operation status, body mass index, and mean age of first coitus. Considering the findings of our study, the difference in rate of HPV regression was not significant in the group with a history of vitamin D use ( $P = 0.804$ ). Regarding metabolic parameters, we observed significant decrease in insulin ( $P < 0.001$ ), triglyceride ( $P = 0.019$ ), and CRP ( $P < 0.001$ ) levels in the group with a history of vitamin D use. **Conclusion:** According to our findings, vitamin D supplementation does not significantly increase the rate of HPV regression. On the other hand, its metabolic effects are noteworthy. It has positive effects on glucose homeostasis and lipid profile. In the light of previous studies, vitamin D may be helpful in the treatment of vaginal infections, nonetheless it is not as effective concerning cervical HPV infections.

## Keywords

Human papillomavirus; Pap smear; Vitamin D

## 1. Introduction

Cervical cancer is one of the most common gynecological cancers in women [1]. HPV plays a major role in neoplastic progression [2]. HPV is the most common sexually transmitted infection in the United States and the highest incidence is seen between the ages 15–25 [3]. Cervical intraepithelial neoplasia (CIN) caused by HPV is precancerous and its progression can result in squamous cell cancer (SCC) [4]. Screening for cervical cancer can begin as early as 21 years of age [3]. Screening programs are of great importance in the prevention of cervical cancer. With the introduction of screening tests for prevention from cervical cancer and early diagnosis, a decrease in mortality rates has been achieved

[5]. As a primary preventive method, the HPV vaccine has been significantly effective [3]. A recent study in Japan also emphasizes the effect of the vaccine on reducing the rate of cervical neoplastic lesions [6]. The relationship between metabolic profile, inflammation biomarkers, oxidative stress, and cervical intraepithelial neoplasia has been demonstrated in previous studies [7–13].

Studies showing the relationship between vitamin D intake and cervical cancer are limited. According to a study conducted in Japan, an inverse relationship was found between calcium and vitamin D intake and the risk of cervical neoplasia [14].  $1\alpha,25(\text{OH})\text{D}_3$  (active metabolite of Vitamin D, calcitriol) has antiproliferative effects according to some preclinical trials [15]. According to the study of Miettinen *et al.*, 25 hydroxyvitamin  $\text{D}_3$  supplements reduced the risk of cancer by regulating calcium metabolism, inhibiting cell proliferation, inducing differentiation, and apoptosis [16]. Another study by Vahedpoor *et al.*, in Iran was focused on cervical lesions [17]. According to their study, vitamin D supplementation both increased the rate of CIN I regression and improved metabolic parameters. These findings provide insight into the role of vitamin D in malignant transformation and proliferation in cervical carcinogenesis.

Vitamin D seems to somewhat improve glycemic regulation; this effect may also reduce progression of cervical neoplasia, given type 2 diabetes is associated with many cancers like cervical cancer [18]. Diabetes Mellitus (DM) and related metabolic disturbances also increase the risk of poor prognosis even for early stage diseases [19, 20]. Therefore, prevention or treatment of DM and related metabolic pathologies are very important regarding cervical neoplasia.

## Objectives

According to the results of previous studies, it suggests that vitamin D may have a role in cervical carcinogenesis. For this reason, we examined the metabolic profile of HPV positive patients, who previously took vitamin D supplements due to vitamin D deficiency and compared it with the patients who did not receive vitamin D supplements. The aim of our study is to evaluate the effects of vitamin D on HPV regres-

sion in vitamin D deficient patients. In this study, the effects of vitamin D on metabolic parameters were also evaluated.

## 2. Materials and methods

The study is a retrospective, cross-sectional, descriptive clinical study. Patients, who visited the outpatient clinic of our department (Dokuz Eylul University Hospital, Department of Obstetrics and Gynecology), between January 2016 and October 2018 were enrolled in our study. The study was approved by the local ethics committee (No: 2019/01-39). Women, who were between 22 and 60 years of age and diagnosed with high-risk HPV by cervical smear, were included. Exclusion criteria were previous diagnosis of malignancy in lower genital tract, smear result indicating HSIL or worse, history of hysterectomy and pregnancy. We collected the following demographic information about study patients: age, presence of comorbidities, body mass index (BMI), age at first coitus, smoking, parity, use of oral contraceptives, chronic immunosuppression and history of any surgery. Patients, who were diagnosed with vitamin D deficiency or had serum vitamin D measurements, were detected from the hospital database. Among them, the ones that received vitamin D<sub>3</sub> supplements containing 300,000 IU oral solution per month for 6 months were identified. Some patients with high-risk HPV were diagnosed with vitamin D deficiency but had not taken supplements according to patient files. Various patients had vitamin D serum measurements and were not prescribed with supplements. We detected 110 patients initially; unfortunately, 10 of them lacked control examinations and therefore excluded. 100 high-risk HPV positive patients were divided into 2 groups as those who received vitamin D supplements (n = 50) and did not receive vitamin D supplements (n = 50). HPV status after the control clinic visit was obtained meanwhile baseline serum vitamin D concentration, lipid profile (total cholesterol, LDL, HDL, triglyceride), fasting insulin concentration, HbA1c, CRP values of the patients were evaluated with the changes in these parameters after 6 months of vitamin D treatment.

### Statistical Analysis

The obtained data were evaluated with SPSS for Windows 15 statistical package program. The frequency of variables and mean and standard deviations of numerical data were calculated by using the Chi-square test and Wilcoxon tests. *P* values below 0.05 were considered statistically significant.

## 3. Results

According to the records, 29 patients were positive with HPV 16, 4 were HPV 18 and 67 were positive with other high-risk subtypes. Cervical cytology results were as follows: 4 LSIL, 4 ASC-US and 92 in normal range. We found no significant difference was found between the patient groups with and without a history of vitamin D intake in terms of age, body mass index, comorbidities, smoking, use of oral contraceptives, and history of previous surgery. There were no immunosuppressed patients in both groups. The parity

rate was found higher in the group without a history of vitamin D use. The difference was statistically significant (*P* = 0.01) (Table 1).

**Table 1. Clinico-pathologic data of the patients.**

	Group	<i>P</i> value
Age (year) (mean ± SD)	Vit D (+) 40.9 ± 10.2	0.99
	Vit D (-) 40.2 ± 8.1	
BMI (kg/m <sup>2</sup> ) (mean ± SD)	Vit D (+) 27.7 ± 0.4	0.66
	Vit D (-) 27.8 ± 0.4	
First coitus age (year) (mean ± SD)	Vit D (+) 22.4 ± 4.4	0.98
	Vit D (-) 23.2 ± 6.7	
Comorbidity existence (n, %)	Vit D (+) 12 (12%)	0.81
	Vit D (-) 11 (11%)	
Comorbidity absence (n, %)	Vit D (+) 38 (38%)	0.41
	Vit D (-) 39 (39%)	
Smoker (n, %)	Vit D (+) 17 (17%)	0.01*
	Vit D (-) 21 (21%)	
Non-smoker (n, %)	Vit D (+) 33 (33%)	0.16
	Vit D (-) 29 (29%)	
Nulliparity (n, %)	Vit D (+) 16 (16%)	0.06
	Vit D (-) 6 (6%)	
Primi-multiparity (n, %)	Vit D (+) 34 (34%)	0.16
	Vit D (-) 44 (44%)	
Oral contraceptive usage (+) (n, %)	Vit D (+) 29 (29%)	0.16
	Vit D (-) 22 (22%)	
Oral contraceptive usage (-) (n, %)	Vit D (+) 21 (21%)	0.06
	Vit D (-) 28 (28%)	
Operation history(+) (n, %)	Vit D (+) 16 (16%)	0.06
	Vit D (-) 25 (25%)	
Operation history (-) (n, %)	Vit D (+) 34 (34%)	0.06
	Vit D (-) 25 (25%)	

Abbreviations: BMI, Body mass index; Vit D, Vitamin D.

Chi-square test was used to evaluate the association between categorical variables. Mann-Whitney U and *T*-test was used to evaluate the association between categorical and continuous variables.

\*: statistically significant.

HPV regression rates and numbers of the patients in our study are shown in Table 2. Data on HPV positive patients with benign smear results were used to compare HPV regressions. Data of 8 patients with abnormal cytology were not included in the HPV regression analysis. (In the vitamin D non-using group, 3 patients had ASC-US, one patient's smear result was LSIL. In vitamin D using group one patient's smear result was ASC-US, and three patients had a smear result LSIL). In the group of patients that did not receive vitamin D, 10 patients were tested negative for HPV after 6 months. The rest of the group was still positive for HPV after their second examination (36 patients). In the group with a history of vitamin D intake, the number of patients who were negative for HPV after 6 months was 11; the rest were tested positive (35 patients). There was no significant difference in HPV regression rates between both groups (*P* = 0.804).

The patients, whose smear results were ASC-US or LSIL,

**Table 2. Effects of vitamin D on HPV regression.**

	Group	Number of patients	P value
HPV regression	No	Vit D (+) (n, %)	35 (38%)
		Vit D (-) (n, %)	36 (39%)
	Yes	Vit D (+) (n, %)	11 (11%)
		Vit D (-) (n, %)	10 (10%)

Abbreviations: HPV, Human papillomavirus; Vit D, Vitamin D.

Chi-square test was used to evaluate the association between HPV regression and vitamin D intake.

were also examined about any cytological improvement. In the group without vitamin D supplementation, two of the three patients with ASC-US had benign cytologies after six months, while one of the ASC-US and the only LSIL results did not change at the second examination. Only one of the patients was tested negative for HPV at the final examination (Her final smear was in normal range). In the patient group with a history of vitamin D intake, three of the smears resulted with LSIL and one with ASC-US. After 6 months, control smear result of 2 patients whose prior smear result was LSIL was detected benign; 1 remained as LSIL. The control smear result of the patient with ASC-US was also benign. One of these four patients were tested negative for HPV (The women, whose prior smear result was LSIL and the control was benign); the other three remained positive.

Table 3 includes the average values of the initial and final values of vitamin D, insulin, HbA1c, total cholesterol, triglyceride, LDL, HDL, CRP of the patients in our study; and the comparison of these values. When the two groups were compared, there was a significant difference between vitamin D initial values ( $P = 0.001$ ), vitamin D final values ( $P < 0.001$ ), HDL final values ( $P = 0.031$ ), CRP initial values ( $P = 0.031$ ). All these four values were found to be higher in the group receiving vitamin D. In patients with a history of vitamin D use, insulin initial and final values ( $P < 0.001$ ), total cholesterol initial and final values ( $P = 0.002$ ), triglyceride initial and final values ( $P = 0.019$ ), between baseline and end values of CRP ( $P < 0.001$ ) were found significantly different. Among these four parameters, the total cholesterol value increased with the use of vitamin D and the values of the other three parameters decreased with the use of vitamin D and all of them were statistically significant. In addition, in both groups, the final vitamin D levels were observed to be higher than the initial values and this increase was found to be statistically significant ( $P < 0.001$ ). There was no significant difference between the two groups in terms of insulin baseline, insulin final, HbA1c baseline, HbA1c final, total cholesterol baseline, total cholesterol final, triglyceride baseline, triglyceride final, HDL baseline, and CRP final values. The change between the baseline and final values of LDL, HDL, HbA1c in both groups was not statistically significant. In the group that did not take vitamin D, the changes between the baseline and final values of insulin, total cholesterol, triglyceride, CRP were also not statistically significant.

## 4. Discussion

This study was mainly constructed to evaluate the effect of vitamin D on the rate of HPV regression among women, who were tested positive for HPV after cervical smears. Studies suggest that vitamin D may have various anticancer effects [15, 21], yet our primary outcome did not reveal a significant effect of vitamin D regarding HPV regression. Data on the relationship between vitamin D and cervical neoplasia are limited. However, the biological mechanism of vitamin D in cancer cells is not fully understood. Vitamin D is metabolized to 1,25-dihydroxyvitamin D<sub>3</sub> [1,25(OH)<sub>2</sub>D<sub>3</sub>], which regulates cell growth and differentiation and the immune system in various tissues. In two studies conducted by Friedrich *et al*, it was shown that the messenger RNA and protein expression of the vitamin D receptor and vitamin D activating enzyme were increased in cervical cancer tissue compared to normal tissues [22, 23]. In the study of Garcia Carrasco *et al.*, the relationship between low serum 25 hydroxyvitamin D<sub>3</sub> level and HPV infection in women with SLE was evaluated [24]. In patients with 25 hydroxyvitamin D<sub>3</sub> level  $< 20$  ng/mL, the prevalence of cervical HPV infection was higher than those with values higher than 20 ng/mL.

In the study conducted by Uebbing *et al.*, data of 200 women with chronic recurrent cervical infections and cervical dysplasia (CIN 1, CIN 2; Uebbing *et al.*, preferred CIN terminology instead of LSIL/HSIL) were evaluated. After 25 hydroxyvitamin D<sub>3</sub> supplementation (12.500 IU, 3 nights a week, 6 weeks vaginal suppository), it was found that condition of most patients improved [25]. Vitamin D had a very good anti-inflammatory effect. Six weeks after the treatment in the CIN 1 group, a very good anti-dysplastic effect was observed, whereas, in the CIN 2 group, a lower anti-dysplastic effect was observed. No significant HPV regression was detected in patients with high-risk HPV. Therefore, the vaginal vitamin D treatment method may be an option for the treatment and prevention of chronic cervical infections and CIN 1. The outcome concerning high risk HPV was similar with our study. Our study could not evaluate improvements in mild cervical dysplasia since the number of cases were very low (records of 4 patients in each group). Nevertheless, not only the study by Uebbing *et al.* but also other literature suggests that vitamin D may not be very effective in HPV regression in patients with high-risk HPV [26].

Vahedpoor *et al.* investigated the effects of long-term administration of vitamin D (50,000 IU vitamin 25 hydroxyvitamin D<sub>3</sub> supplement every 2 weeks for 6 months) on regression and metabolic status of patients with CIN 1 cervical biopsy result. Vitamin D supplementation was determined resulting in CIN 1 regression. In addition, a significant decrease was found in insulin and lipid concentrations [17]. Again, we could not assess the cytological changes after vitamin D intake, but the changes in metabolic parameters were similar in our study. Concerning metabolic benefits of vitamin D, according to the study by Asemi *et al.*, it was found that intake of 1250 µg/week for 8 weeks in normal or obese

**Table 3. Effects of vitamin D on metabolic parameters.**

	Group		P value
Vitamin D baseline level (ng/mL)	Vit D (+)	16.2 ± 8.2	< 0.01*
	Vit D (-)	12.7 ± 13.0	
Vitamin D final level (ng/mL)	Vit D (+)	23.6 ± 6.4	< 0.01*
	Vit D (-)	14.5 ± 13.2	
Vit D alteration in Vit D (+) group			< 0.01*
Vit D alteration in Vit D (-) group			< 0.01*
Insulin baseline level (mIU/mL)	Vit D (+)	14.0 ± 10.6	0.96
	Vit D (-)	16.6 ± 13.5	
Insulin final level (mIU/mL)	Vit D (+)	11.1 ± 7.7	0.18
	Vit D (-)	15.1 ± 13.2	
Insulin alteration in Vit D (+) group			< 0.01*
Insulin alteration in Vit D (-) group			0.3
HbA1c baseline level (% mmol/mol)	Vit D (+)	5.3 ± 0.4	0.43
	Vit D (-)	5.4 ± 0.8	
HbA1c final level (% mmol/mol)	Vit D (+)	5.2 ± 0.4	0.78
	Vit D (-)	5.3 ± 0.7	
HbA1c alteration in Vit D (+) group			0.09
HbA1c alteration in Vit D (-) group			0.13
Total Cholesterol baseline level (mg/dL)	Vit D (+)	197.4 ± 33.9	0.44
	Vit D (-)	200.8 ± 41.5	
Total cholesterol final level (mg/dL)	Vit D (+)	198.5 ± 33.1	0.64
	Vit D (-)	200.8 ± 40.4	
Total cholesterol alteration in Vit D (+) group			< 0.01*
Total cholesterol alteration in Vit D (-) group			0.89
Triglyceride baseline level (mg/dL)	Vit D (+)	129.1 ± 70.6	0.42
	Vit D (-)	139.3 ± 84.4	
Triglyceride final level (mg/dL)	Vit D (+)	122.2 ± 45.8	0.76
	Vit D (-)	143.1 ± 83.7	
Triglyceride alteration in Vit D (+) group			0.01*
Triglyceride alteration in Vit D (-) group			0.39
LDL baseline level (mg/dL)	Vit D (+)	134.0 ± 127.7	0.55
	Vit D (-)	114.8 ± 37.5	
LDL final level (mg/dL)	Vit D (+)	119.7 ± 46.7	0.58
	Vit D (-)	113.4 ± 32.6	
LDL alteration in Vit D (+) group			0.24
LDL alteration in Vit D (-) group			0.3
HDL baseline level (mg/dL)	Vit D (+)	60.1 ± 10.3	0.06
	Vit D (-)	55.4 ± 11.5	
HDL final level (mg/dL)	Vit D (+)	61.4 ± 10.7	0.03*
	Vit D (-)	56.0 ± 10.7	
HDL alteration in Vit D (+) group			0.06
HDL alteration in Vit D (-) group			0.76
CRP baseline level (mg/L)	Vit D (+)	5.2 ± 4.2	0.03*
	Vit D (-)	3.7 ± 3.6	
CRP final level (mg/L)	Vit D (+)	4.5 ± 3.5	0.17
	Vit D (-)	3.4 ± 2.6	
CRP alteration in Vit D (+) group			< 0.01*
CRP alteration in Vit D (-) group			0.45

Abbreviations: Vit D, Vitamin D; HbA1c, Hemoglobin A1c; HDL, High density lipoprotein; LDL, Low density lipoprotein; CRP, C-reactive protein.

Chi-square test was used to evaluate the association between categorical variables. Mann-Whitney U and T-test was used to evaluate the association between categorical and continuous variables.

\*: statistically significant.

men and 100,000 IU 25 hydroxyvitamin D<sub>3</sub> for 6 weeks in women with a diagnosis of gestational diabetes, the markers related to glycemic regulation and also serum lipid concentrations improved [27]. However, some studies did not report the positive effects of vitamin D supplementation on glucose homeostasis parameters. According to the study by Javed *et al.*, 400 IU or 2000 IU of 25 hydroxyvitamin D<sub>3</sub> supplementation per day for 12 weeks did not affect  $\beta$  cell function or insulin function in obese non-diabetic adolescents with relatively good vitamin D status [28].

In addition, according to the study of Chandler *et al.*, 1000, 2000, or 4000 IU/day oral intake of 25 hydroxyvitamin D<sub>3</sub> for 3 months did not cause a significant change in CRP concentrations [29]. However, baseline CRP concentrations were significantly higher in patients with vitamin D deficiency. In our study, a significant decrease was found in insulin, triglyceride, and CRP values in the group with a history of vitamin D intake. The patients in our group had taken a higher amount of vitamin D for a longer period. Therefore, the decrease in CRP may confirm the baseline CRP results of the study by Chandler *et al.*

The baseline vitamin D levels of patients, who did not receive vitamin D supplementation, was lower than the ones that received supplementation. There are various explanations for this finding. First of all, the prevalence of vitamin D deficiency is very high in Turkey although the climate permits plentiful sunlight exposure; due to many reasons like type of clothing and other factors [30]. One of the studies was conducted in a city geographically close to our institution has also reached similar findings [31]. Many of the patients that took supplements had previously taken vitamin D while the patients in the control group had not been receiving medication before their first visit. Some patients in the control group were prescribed but did not use the medication. We think that these were the main reasons for this difference. Keeping in mind that vitamin D deficiency is very common in the country, mean baseline levels for both groups were below 20 ng/dL.

The study was a single-center study and the data was studied at the same institution. The hospital's electronic registry has extensive and reliable information regarding patient histories. These features are strengths of the study. The retrospective design and the low number of patients are weaknesses of the study. Especially it was not possible to assess the changes in cytologic results due to scarcity of patients with ASC-US or LSIL. Prospective studies with larger patient numbers ought to be conducted to obtain more reliable findings.

## 5. Conclusions

Vitamin D plays an important role in metabolic processes, prevention of carcinogenic processes and many other biological activities. The pathways for these effects are far from being completely enlightened. Our study did not achieve to show an increased rate of HPV regression in patients tak-

ing vitamin D supplementation. Nevertheless, our study was mostly in parallel with other studies concerning the metabolic benefits that vitamin D supplementation provides. At this point, we think that it is safe to say that correction of vitamin D deficiency is very important to improve metabolic parameters and since metabolic disorders increase the risk of cervical cancer, vitamin D supplementation is important to reduce the risk. Unfortunately, current data does not indicate a strong association between vitamin D levels and HPV regression. Prospective studies with larger patient groups will provide more information.

## Author contributions

SK: Concept, Design, Literature search, Critical review. SuK: Data collection and processing, analysis and interpretation of data, Writing manuscript, Critical review. OI: Analysis and interpretation of data, Writing manuscript, Critical review. HTT: Writing manuscript, critical review. TU: Supervision, Concept, Critical review.

## Ethics approval and consent to participate

The study was approved by the local ethics committee of Dokuz Eylul University School of Medicine (No: 2019/01-39).

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## Conflict of interest

The authors declare no conflict of interest.

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