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Is Prostate Cancer Related to Low Vitamin D Level?

Aytaç Şahin MD[1], Tuncay Toprak MD[1], Musab Ali Kutluhan MD[1], Ahmet Ürkmez MD[2], Çağlar Yıldırım[3], Ayhan Verit MD[1]

[1] *Fatih Sultan Mehmet Training and Research Hospital, Clinic of Urology, İstanbul, Turkey*
[2] *Haydarpaşa Numune Training and Research Hospital, Clinic of Urology, İstanbul, Turkey*
[3] *Mardin State Hospital, Clinic of Urology, Mardin, Turkey*

Abstract

Objective: Prostate cancer (PC) is the most common malignancy among men worldwide. There are several epidemiological studies linking the risk and outcome of vitamin D with PC. In this study, we aimed to compare vitamin D levels in patients with PC and benign prostatic hyperplasia (BPH).
Materials and Methods: Patients with PC and BPH admitted to our urology outpatient clinic between 2017 and 2019 were included in this case-control study. Serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels were measured to assess vitamin D status.
Results: The study was conducted with a total of 256 patients aged between 47 and 86 years between 2018-2019. The mean age of 128 patients with PC was 67.70±7.74 years, and the mean age of 128 patients with BPH was 67.03±7.89 years. There was a statistically significant difference between patients with PC and BPH in terms of 25-hydroxyvitamin D levels. When the patients diagnosed with PC were examined according to their subgroups, the mean 25-hydroxyvitamin D levels of 64 patients with ISUP Grade I tumors were significantly higher than the remaining 64 patients with ISUP Grade II, III and IV tumors.
Conclusion: According to our results, vitamin D levels were found to be significantly lower in patients with PC than in patients with BPH, and a significant decrease was found in vitamin D levels as the Gleason score increased. Since PC has a high prevalence and heterogeneous geographical distribution, randomized controlled trials are needed in order to demonstrate the relationship between vitamin D and cancer.
Keywords: Vitamin D, prostate cancer, benign prostatic hyperplasia

Introduction

Prostate cancer (PC) is the most common malignancy among men worldwide (1). In addition, the incidence of PC increased significantly in most Asian populations (2). New molecularly targeted therapies for PC patients have improved over the last 10 years (3,4). There are a limited number of modifiable risk factors identified for PC, and further studies are needed to identify some modifiable risk factors associated with PC. There are numerous epidemiological studies linking the risk and outcome of vitamin D with PC (5,6,7,8). Vitamin D is a steroid prohormone that dissolves in fat and is produced in skin by contact with sunlight. With various metabolic changes in the body, it becomes a hormone known as calcitriol, which plays an important role in calcium and phosphate metabolism. In addition to having an important role in many mechanisms in the body, Vitamin D deficiency can cause many adverse conditions.

In addition to its association with major public health problems such as obesity, diabetes, and hypertension, recent studies focus on the relationship between vitamin D and cancer with increasing prevalence and types. In addition, studies have been conducted on the anti-cancer effects of vitamin D as well as the effects that suppress cancer cell growth (9). In this study, we aimed to investigate whether there is a statistically significant difference between vitamin D levels in patients with PC and patients with benign prostatic hyperplasia (BPH).

Materials and Methods

This case-control study was initiated with the approval of Fatih Sultan Mehmet Training and Research Hospital Ethics Committee (Number: FSMEAH-KAEK 2017/6, date: 12.01.2017) and each patient included in the study signed informed consent form. Patients diagnosed with PC and BPH who admitted to our urology outpatient clinic between 2017 and 2019 were included in the study. The cases were newly diagnosed, followed-up and histopathologically proven PCs. Patients with metastatic PC, recent severe weight loss, and who underwent hormonal therapy or finasteride treatment were excluded. The control group consisted of patients with lower urinary

Address for Correspondence: Aytaç Şahin MD, Fatih Sultan Mehmet Training and Research Hospital, Clinic of Urology, İstanbul, Turkey
Phone: +90 216 578 30 00 **E-mail:** draytacsahin@gmail.com **ORCID:** orcid.org/0000-0003-4373-8104
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tract symptoms who had no pathology on digital rectal examination (DRE) and had a PSA level <2.0 ng/mL. Serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels were measured to assess vitamin D status. Vitamin D concentration was evaluated by ultra-performance liquid chromatography/ tandem spectrometry analysis.

Statistical Analysis

IBM SPSS Statistics 25 program was used for statistical analysis. When evaluating the study data, the normality of the parameters was evaluated with Shapiro-Wilk test. The descriptive statistical methods included mean and standard deviation, and Student-t test was used for the comparison of parameters with normal distribution. Significance was evaluated at p<0.05.

Results

The study was conducted with a total of 256 patients aged between 47 and 86 years between 2018-2019. The mean age of 128 patients with PC was 67.70±7.74 years, and the mean age of 128 patients with BPH was 67.03±7.89 years (Table 1). There was no statistically significant difference between patients with PC and BPH in terms of age (p>0.05).

Although the mean 1,25-dihydroxyvitamin D level in patients with PC was lower than those with BPH, no statistically significant difference was found (p>0.05). There was a statistically significant difference between both groups in terms of 25-hydroxyvitamin D levels (p=0.000). When the patients diagnosed with PC were examined according to their subgroups, the mean 1,25-hydroxyvitamin D levels of 64 patients with ISUP Grade I tumors were higher than the remaining 64 patients with ISUP Grade II, III and IV tumors, however, no statistically significant difference was found (p>0.05). When the patients diagnosed with PC were examined according to their subgroups, the mean 25-hydroxyvitamin D levels of 64 patients with ISUP Grade I tumors were significantly higher than the remaining 64 patients with ISUP Grade II, III and IV tumors (p<0.01) (Table 2).

Discussion

Although vitamin D has preventive roles in many cancers, its role in the development of PC is still unclear. In the human body, vitamin D is synthesized mainly in the skin after exposure to sunlight and also vitamin D can be taken from some foods (10,11). 25-hydroxyvitamin D, which is the most widely used biological form of circulating vitamin D, is the hydroxylated form of vitamin D and is widely used in clinical practice (12). It is then converted to the biologically active 1,25-hydroxyvitamin D (calcitriol) by 1-alpha-hydroxylase enzyme in the kidney and other tissues, including the prostate (13). The biomarker of vitamin D in humans is mainly 25-hydroxyvitamin D and partly 1,25-hydroxyvitamin D, and studies have been based on these indicators regarding vitamin D serum levels (14). Vitamin D serum level less than 20 ng/mL (50 nmol/L) is defined as inadequacy (15).

Table 1. Comparison of prostate cancer and benign prostate hyperplasia patients

	PC (n=128)	BPH (n=128)	p value
	Mean ± SD	Mean ± SD	
Age (years)	67.70±7.74	67.03±7.89	**0.498**
1,25-hydroxyvitamin D (ng/mL)	29.42±13.99	31.28±13.64	**0.283**
25-hydroxyvitamin D (ng/mL)	19.45±7.24	26.15±8.80	**0.000***

Independent samples t-test *p<0.05
PC: Prostate cancer, BPH: Benign prostate hyperplasia, SD: Standard deviation

In epidemiological studies on vitamin D levels of cancer patients, it is stated that these levels are less than normal values (16). Vitamin D has been shown to cause dysfunction or inhibition of cell proliferation of PC cells, cell invasion, angiogenesis and altered gene expression, including c-Myc and telomerase expression, or induction of cell differentiation and apoptosis (17,18,19,20). *In vitro* cell culture and *in vivo* animal studies have shown that active vitamin D increases cell differentiation, inhibits cancer cell proliferation, and exhibits anti-inflammatory, pro-apoptotic and anti-angiogenic properties. In laboratory studies, it has been shown that active vitamin D inhibits the growth of cancer cells by binding to vitamin D receptor (VDR) and regulating various genes responsible for cell proliferation (21,22,23). Active vitamin D stimulates the expression of cell cycle inhibitors p21 and p27, and the expression of the cell adhesion molecule E-cadherin. It inhibits the transcriptional activity of α-catenin. Active vitamin D in keratinocytes has been shown to increase repair of DNA damage caused by UVR, reduce apoptosis, and increase p53 (16). Some studies (18,24,25,26) support the idea that high serum Vitamin D levels have protective effects. Other studies have shown different results (27,28). In a meta-analysis focusing on the relationship between 25-hydroxyvitamin D and mortality in PC, a study of 7808 participants was conducted, and the results calculated from seven eligible studies showed a significant correlation with higher vitamin D levels and a reduction in all-cause mortality and a reduction in PC-related mortality. Other dose-response analysis showed that every 20 nmol/L increase in 25-hydroxyvitamin D level was associated with a 9% lower risk of all-cause mortality and PC-related mortality. It was concluded that high levels of circulating vitamin D were associated with a lower risk of PC-related mortality (29).

A meta-analysis of 21 studies by Xu et al. (30) found a high risk of developing PC in patients with a high level of 25-hydroxyvitamin D in the serum. Sixteen studies showed a positive correlation between serum vitamin D level and PC [odds ratio (OR)=1.17, 95% confidence interval: 1.08-1.27].

Table 2. Comparison of prostate cancer subgroups

	ISUP 1 (n=64)	ISUP 2,3,4 (n=64)	p value
	Mean ± SD	Mean ± SD	
1,25-hydroxyvitamin D (ng/mL)	30.86±11.49	27.99±16.07	**0.247**
25-hydroxyvitamin D (ng/mL)	22.13±7.26	16.76±6.20	**0.000***

Independent samples t-test *p<0.05
ISUP: International Society of Urological Pathology, SD: Standart deviation

In one study, it was shown that the incidence of PC was high and vitamin D level was low in the black race compared to other races (31). Selenium and vitamin E cancer protection research found an inverse relationship between plasma vitamin D levels in high-grade cancers with a Gleason score of 7-10 (32).

In our study, there was a statistically significant difference between patients with PC and BPH in terms of mean 25-hydroxyvitamin D levels (p=0.000). In the PC group, 25-hydroxyvitamin D levels were significantly lower. When the patients diagnosed with PC were examined according to their subgroups, the mean 25-hydroxyvitamin D levels of 64 patients with ISUP Grade I tumors were significantly higher than the remaining 64 patients with ISUP Grade II, III and IV tumors (p<0.01). As the Gleason score of cancer increased, a significant decrease was found in vitamin D levels.

In a study conducted since the functions of the VDR and associated vitamin D metabolic enzymes are associated with vitamin D levels, it was shown that nucleotide polymorphisms alone in the 3'-untranslated region of the *VDR* gene were associated with PC risk in men with low vitamin D levels (31).

In a meta-analysis of 19 prospective studies, epidemiological evidence of the tumor-promoting effect of vitamin D in PC was provided, but the effect was modest (32). However, no clear biological relationship was found between high levels of vitamin D and increased risk of PC. We can only speculate about the cause of the tumor-stimulating effect of vitamin D in PC (33). One reason for this may be that 25-hydroxyvitamin D is a sign of other factors related to PC risk. For example, insulin-like growth factor-I (IGF-1) is associated with PC (34,35) and a relationship between 25-hydroxyvitamin D and IGF-1 has been reported. In another study, each 10 ng/mL 25-hydroxyvitamin D increase was associated with an increased risk of PK of 23% (5). In the meta-analysis of Gilbert et al. (36), it was shown that there was a low level of evidence between low exposure to sunlight and the risk of PC (37,38).

Conclusion

According to our results, vitamin D levels were found to be significantly lower in patients with PC than in patients with BPH. In addition, when the cancer group was evaluated among themselves, a significant decrease was found in vitamin D levels as the Gleason score increased. Although there is no relationship between vitamin D and PC in most studies, there are studies in the literature showing an inverse relationship. Since PC has a high prevalence and heterogeneous geographical distribution, randomized controlled trials are needed in order to demonstrate the relationship between vitamin D and cancer.

Ethics

Ethics Committee Approval: This case-control study was initiated with the approval of Fatih Sultan Mehmet Training and Research Hospital Ethics Committee (Number: FSMEAH-KAEK 2017/6, date: 12.01.2017).

Informed Consent: Each patient included in the study signed informed consent form.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.Ş., M.A.K., Concept: A.Ü., Design: T.T., Data Collection or Processing: A.Ş., Ç.Y., Analysis or Interpretation: A.V., A.Ü., Literature Search: A.Ş., Writing: A.Ş.

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